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Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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TITLE OF THE INVENTION (500 characters max)

CRYSTALS AND STRUCTURES OF p21-ACTIVATED KINASE 6

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification   *Number of Pages*   97   ☐ CD(s), Number _____

☒ Drawing(s)   *Number of Sheets*   47   Other (specify)   postcard, title page

☐ Application Data Sheet.   *See 37 CFR 1.76*

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

FILING FEE AMOUNT ($)

☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 501931 $80.00

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

	DATE	February 23, 2004

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Docket Number: PT145/01.PRO

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

CERTIFICATE OF MAILING (37 CFR 1.10)

I hereby certify that the attached Provisional Application Cover Sheet and associated documents attached thereto are being deposited with the United States Postal Service on this date in an envelope as "Express Mail Post Office to Addressee" addressed to: Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Diana Neuner

NEW APPLICATION

THE UNITED STATES

PATENT AND TRADEMARK OFFICE

FOR

CRYSTALS AND STRUCTURES OF p21-ACTIVATED KINASE 6

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CRYSTALS AND STRUCTURES OF p21-ACTIVATED KINASE 6

INTRODUCTION

[0001]   The present invention concerns crystalline forms of polypeptides that correspond to the kinase domain of p21-activated kinase 6 (PAK6KD), methods of obtaining such crystals, and to the high-resolution X-ray diffraction structures and molecular structure coordinates obtained therefrom. The crystals of the invention and the atomic structural information obtained therefrom are useful, for example, for solving the crystal and solution structures of related and unrelated proteins, for screening for, identifying, and/or designing protein analogues and modified proteins, and for screening for, identifying and/or designing compounds that bind to and/or modulate a biological activity of PAK6, including inhibitors and activators of PAK6 activity.

[0002]   PAK6 (p21-activated kinase 6) is a kinase in the STE group of serine/threonine kinases. It is a member of the group II PAKs, which comprises PAK4, PAK5, and PAK6 (Jaffer, Z. M., and Chernoff, J., *J. Biochem Cell Bio.*, 34:713-717, 2002). The PAKs contain an N-terminal p21-Rho-binding domain and a C-terminal catalytic protein kinase domain. Both PAK groups have been implicated in actin reorganization, gene transcription, and apoptosis, while the group II PAKs have also been implicated in cell transformation and hormone signaling (Jaffer and Chernoff, 2002). PAK6 interacts with at least two nuclear hormone receptors; it is recruited to the nucleus in the presence of ligand-bound androgen receptor (AR) (Yang, F., et al., *J. Biol. Chem*, 276:15345-15353, 2001) and it is able to bind Erα (Lee, S. R., et al., *Mol. Endocrinol.* 16:85-99, 2002). Binding of PAK6 to AR appears to repress transcription by preventing coactivator binding. This may be a novel mechanism within the PAK family and has implications for the treatment of prostate and breast cancer. Unphosphorylated (active) PAK6 has recently been shown to be differentially expressed in prostate cancer cell lines (Schrantz, N., et al., *J. Biol. Chem*, 279:1922-1931, 2004).

[0003]   The present invention describes the 3-dimensional structure of the kinase domain of PAK6 (PAK6KD). The 3 dimensional structure of PAK6 may be useful, for example, for identifying novel therapeutic compounds that can modulate protein kinase activity, and for treatment of diseases or conditions mediated by human signal transduction kinase activity, or diseases or conditions that may be alleviated or prevented

by modulation of, PAK6 activity, and/or, for example, actin reorganization, gene transcription, apoptosis, hormone signaling, or cell transformation.

[0004]   Knowledge of the 3-D structures of target proteins provides an important basis for structure-based approaches to drug design by defining the topographies of the complementary surfaces of ligands and their protein targets. Therefore, knowledge of the structure of the PAK6KD protein described in the present invention may be useful in the identification, design, or development of novel and specific modulators of protein kinase activity as well as diagnostic and pharmaceutical compounds useful for disorders associated with aberrant PAK6 expression or activity. Knowledge of the structure may also be useful for gene therapy. The structural coordinates may be used, for example, to engineer more stable or other modified PAK6s. The ability to obtain the molecular structure coordinates of PAK6KD has not previously been realized.

[0005]   Citation of documents herein is not intended as an admission that any is pertinent prior art. All statements as to the date or representation as to the contents of documents is based on the information available to the applicant and does not constitute any admission as to the correctness of the dates or contents of the documents.

SUMMARY OF THE INVENTION

[0006]   The present invention provides crystalline PAK6KD, its molecular structure in atomic detail, homologs and mutants of the structure, methods of using the structure to identify and design compounds that modulate the activity of PAK6, methods of preparing identified and/or designed compounds, methods of affecting cell growth and/or viability, and thus treating diseases or conditions, by modulating PAK6 activity, and methods of identifying and designing mutant PAK6s. Knowledge of the structure of PAK6KD may be useful in the development of novel compounds regulating, for example, cell proliferation, cell migration, differentiation, cytoskeletal organization, gene expression, cell cycle progression, and cell death. Knowledge of the structure of PAK6KD may also be used to model the structure of kinases with related ligand binding sites, such as, for example, other PAKs.

[0007]   By "PAK6 activity" is meant PAK6 kinase activity, binding activity, imunogenicity, or any enzymatic activity of the PAK6 protein, or the PAK6 kinase domain alone. Thus, PAK6 activity may be assayed, where appropriate, using all or a portion of the entire PAK6 molecule. For example, the PAK6 kinase domain alone may be used in

kinase, binding, immunogenicity, or other PAK6 enzymatic activities. Similarly, a modulator, inhibitor, or activator of PAK6 protein may also be a modulator, inhibitor, or activator of the PAK6 kinase domain, and modulation, inhibition or activation of PAK6 activity may be assayed by assaying the modulation, inhibition, or activation of PAK6 kinase domain activity. Also, where PAK6KD activity is assayed, portions of the PAK6 molecule in addition to the PAK6KD may be used in the assay. Thus, for example, where the present invention describes assaying modulation, inhibition, or activation of PAK6KD, instead, an assay may be performed to determine modulation, inhibition, or activation of PAK6.

[0008]   Thus, in one aspect, the invention provides purified PAK6KD, and methods of purifying PAK6KD. PAK6KD may be sufficiently pure such that it may be used to prepare diffraction quality crystals. For ease of obtaining diffraction quality crystals, the purified PAK6KD may be predominantly, or entirely, of one phosphorylation state.

[0009]   Thus, in one aspect, the invention provides a crystal comprising PAK6 or PAK6KD peptides in preferred crystalline form. In some embodiments of the invention the crystal is diffraction quality. The crystals of the invention include, for example, crystals of wild type PAK6KD, crystals of mutated PAK6KD, native crystals, heavy-atom derivative crystals, and crystals of PAK6KD homologs or PAK6KD mutants, such as, but not limited to, selenomethionine or selenocysteine mutants, mutants comprising conservative alterations in amino acid residues, and truncated or extended mutants.

[0010]   The crystals of the invention also include co-crystals, in which crystallized PAK6KD is in association with one or more compounds, including but not limited to, cofactors, ligands, substrates, substrate analogs, inhibitors, activators, agonists, antagonists, modulators, allosteric effectors, etc., to form a crystalline co-complex. Such compounds may or may not bind a catalytic or active site of PAK6KD within the crystal. Alternatively, such compounds stably interact with another binding pocket of PAK6KD within the crystal. The co-crystals may be native co-crystals, in which the co-complex is substantially pure, or they may be heavy-atom derivative co-crystals, in which the co-complex is in association with one or more heavy-metal atoms, preferably heavy-metal atoms that promote anomalous scattering.

[0011]   In other embodiments, the crystals of the invention are of sufficient quality to permit the determination of the three-dimensional X-ray diffraction structure of the crystalline polypeptide to high resolution, for example, to a resolution of better than 3Å,

or, at least 1Å and up to about 3Å, and more typically a resolution of greater than 1.5Å and up to 2Å or about 2Å, or 2.5Å or about 2.5Å.

[0012] In some embodiments, the crystals are characterized by a unit cell of a= 59.2Å+/- 2%, b= 66.7Å +/- 2%, c= 97.2Å+/- 2%, α= 90°, β= 90°, γ= 90°, and a space group of P 21 21 21.

[0013] The invention also provides methods of making the crystals of the invention. Generally, crystals of the invention are grown by dissolving substantially pure polypeptide in an aqueous buffer that includes a precipitant at a concentration just below that necessary to precipitate the polypeptide. Water is then removed by controlled evaporation to produce precipitating conditions, which are maintained until the crystal forms and the size of the crystal is appropriate.

[0014] Co-crystals of the invention are prepared by soaking a native crystal prepared according to the above method in a liquor comprising the compound of the desired co-complex. Alternatively, the co-crystals may be prepared by co-crystallizing the polypeptide in the presence of the compound according to the method discussed above.

[0015] Heavy-atom derivative crystals of the invention may be prepared by soaking native crystals or co-crystals prepared according to the above method in a liquor comprising a salt of a heavy atom or an organometallic compound. Alternatively, heavy-atom derivative crystals may be prepared by crystallizing a polypeptide comprising modified amino acids, for example, selenomethionine and/or selenocysteine residues according to the methods described above for preparing native crystals.

[0016] In yet another embodiment of the present invention, a method is provided for determining the three-dimensional structure of a PAK6KD crystal, comprising the steps of providing a crystal of the present invention; and analyzing the crystal by x-ray diffraction to determine the three-dimensional structure. Stated differently, the invention provides for the production of three-dimensional structural information (or "data") from the crystals of the invention. Such information may be in the form of structural coordinates that define the three-dimensional structure of PAK6KD in a crystal and/or co-crystal. Alternatively, the structural coordinates may define the three-dimensional structure of a portion of PAK6KD in the crystal. Non-limiting examples of portions of PAK6KD include the catalytic or active site, and a binding pocket. The structural coordinate information may include other structural information, such as vector representations of the molecular

structures coordinates, and be stored or compiled in the form of a database, optionally in electronic form.

[0017] The invention thus provides methods of producing a computer readable database comprising the three-dimensional molecular structural coordinates of binding pocket of PAK6KD, said methods comprising obtaining three-dimensional structural coordinates defining PAK6KD or a binding pocket of PAK6KD, from a crystal of PAK6KD; and introducing said structural coordinates into a computer to produce a database containing the molecular structural coordinates of PAK6KD or said binding pocket. The invention also provides databases produced by such methods.

[0018] In an alternative embodiment, the invention provides for the use of identifiers of structural information to be all or part of the information defining the three-dimensional structure of PAK6KD so that all or part of the actual structural information need not be present. For example, and without limiting the invention, identifiers which reference structural coordinates defining a three-dimensional structure, substructure or shape may be used in place of the actual coordinate information. Such reference structural information is optionally stored separately from the identifiers used to define the three-dimensional structure of PAK6KD. A non-limiting example is the use of an identifier for an alpha helix structure in place of the coordinates of the helical structure, or the use of distances and angles to represent the structure.

[0019] In another aspect, the invention provides computer machine-readable media embedded with the three-dimensional structural information obtained from the crystals of the invention, or portions or substrates thereof. The invention also provides methods for the introduction of the structural information into a computer readable medium, optionally as a computer readable database. The types of machine- or computer-readable media into which the structural information is embedded typically include magnetic tape, floppy discs, hard disc storage media, optical discs, CD-ROM, electrical storage media such as RAM or ROM, and hybrids of any of these storage media. Such media further include paper that may be read by a scanning device and converted into a three-dimensional structure with, for example, optical character recognition (OCR) software. In one example, the sheet of paper presents the molecular structure coordinates of crystalline polypeptide of the invention that are converted into, for example, a spread sheet by OCR software. The machine-readable media of the invention may further comprise additional

information that is useful for representing the three-dimensional structure, including, but not limited to, thermal parameters, chain identifiers, and connectivity information.

[0020]   Various machine-readable media are provided in the present invention. In one aspect, a machine-readable medium is provided that is embedded with information defining a three-dimensional structural representation of any of the crystals of the present invention, or a fragment or portion thereof. The information may be in the form of molecular structure coordinates, such as, for example, those of Fig. 4. Alternatively, the information may include an identifier used to reference a particular three dimensional structure, substructure or shape. The machine-readable medium may be embedded with the molecular structure coordinates of a protein molecule comprising a PAK6KD active site, active site homolog, binding pocket or binding pocket homolog. The various machine-readable media of the present invention may also comprise data corresponding to a molecule comprising a PAK6KD binding pocket or binding pocket homolog in association with a compound or molecule bound to the protein, such as in a co-crystal.

[0021]   The molecular structure coordinates and machine-readable media of the invention have a variety of uses. For example, the coordinates are useful for solving the three-dimensional X-ray diffraction and/or solution structures of other proteins, including mutant PAK6KD, co-complexes comprising PAK6KD, and unrelated proteins, to high resolution. Structural information may also be used in a variety of molecular modeling and computer-based screening applications to, for example, intelligently design mutants of the crystallized PAK6KD that have altered biological activity and to computationally design and identify compounds that bind the polypeptide or a portion or fragment of the polypeptide, such as a subunit, a domain or an active site. Such compounds may be used directly or as lead compounds in pharmaceutical efforts to identify compounds that affect PAK6KD activity. Compounds that bind to the polypeptide, or to a portion or fragment thereof may be used as, for example, antimicrobial agents.

[0022]   The invention thus provides methods of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of PAK6KD, said methods comprising introducing into a computer program a computer readable database comprising structural coordinates which may be used to produce a three dimensional representation of PAK6KD, generating a three-dimensional representation of a binding pocket of PAK6KD in said computer program, superimposing a three-dimensional model of at least one binding test compound on said representation of the

binding pocket, assessing whether said test compound model fits spatially into the binding pocket of PAK6KD and storing a representation of a compound that fits into the binding pocket into a computer readable database. The database used to store the representation of a compound may be the same or different from that used to store the structural coordinates of PAK6KD. The invention further provides for the electronic transmission of any structural information resulting from the practice of the invention, such as by telephonic, computer implemented, microwave mediated, and satellite mediated means as non-limiting examples.

[0023]   As described above, the molecular structure coordinates and/or machine-readable media associated with PAK6KD structure may also be used in the production of three-dimensional structural information (or "data") of a compound capable of binding PAK6KD. Such information may be in the form of structural coordinates that define the three-dimensional structure of a compound, optionally in combination or with reference to structural components of PAK6KD. In some embodiments, the structure coordinates of the compound are determined and presented (or represented) relative to the structure coordinates of the protein. Alternatively, identifiers of structural information are used to represent all or part of the information defining the three-dimensional structure of a compound so that all or part of the actual structural information need not be present. For example, and without limiting the invention, if the structural information of a compound includes a region defining a pyrophosphate (or pyrophosphate mimetic) moiety, the structural coordinates of pyrophosphate may be substituted by an identifier representing the structure of pyrophosphate, such as the name, chemical formula or other chemical representation. Any compound capable of binding PAK6KD may be represented by chemical name, chemical or molecular formula, chemical structure, and/or other identifying information. As a non-limiting example, the compound CH_3CH_2OH may be represented by names such as ethanol or ethyl alcohol, abbreviations such as EtOH, chemical or molecular formulas such as CH_3CH_2OH or C_2H_5OH or C_2H_6O, and/or by structural representations in two or three dimensions. Non-limiting examples of the latter include Fisher projections, electron density maps and representations, space filling models, and the following:

CH$_3$——CH$_2$-OH   H$_3$C——C——OH
                              H$_2$
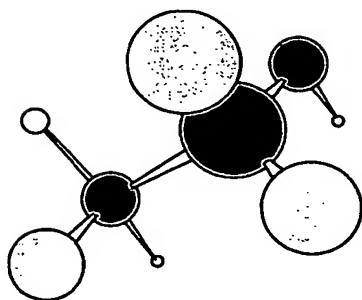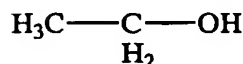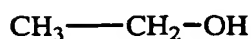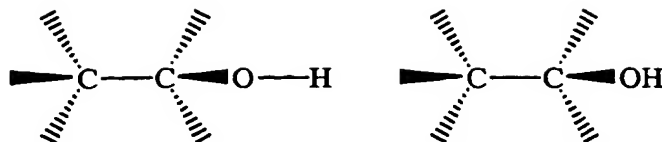
[0024] Non-limiting examples of other identifying information include Chemical Abstract Service (CAS) Registry numbers and physical or chemical properties indicative of the compound (such as, but not limited to, NMR spectra, IR spectra, MS spectra, GC profiles, and melting point). Of course the structures of a portion of a compound (e.g. a substructure) may be similarly identified by reference to any of the above used to identify a compound as a whole.

[0025] To produce structural information of a compound capable of binding PAK6KD, the invention provides for the use of a variety of methods, including a) the superimposition of structures of known compounds on the structure of PAK6KD or a portion thereof, b) the determination of a "pharmacophore" structure which binds PAK6KD, and c) the determination of substructure(s) of compounds, wherein the substructure(s) interact with PAK6KD. The structural coordinate information may include other structural information, such as vector representations of the molecular structures coordinates, and be stored or compiled in the form of a database, optionally in electronic form. With respect to a), the invention includes the computational screening of a three-dimensional structural representation of PAK6KD or a portion thereof, or a molecule comprising a PAK6KD binding pocket or binding pocket homolog, with a plurality of chemical compounds and chemical entities. Alternatively, the present invention provides a method of identifying at least one compound that potentially binds to PAK6KD, comprising, constructing a three-

dimensional structure of a protein molecule comprising a PAK6KD binding pocket or binding pocket homolog, or constructing a three-dimensional structure of a molecule comprising a PAK6KD binding pocket, and computationally screening a plurality of compounds using the constructed structure, and identifying at least one compound that computationally binds to the structure. In one aspect, the method further comprises determining whether the compound binds PAK6KD.

[0026]   With respect to b) the invention includes the computational screening of a plurality of chemical compounds to determine which compound(s), or portion(s) thereof, fit a pharmacophore determined as fitting within a PAK6KD binding pocket. Stated differently, the structures of chemical compounds may be screened to identify which compound(s), or portion(s) thereof, is encompassed by the parameters of an identified pharmacophore. As used herein, "pharmacophore" refers to the structural characteristics determined as necessary for a chemical moiety to fit or bind a PAK6KD binding pocket. A non-limiting example of a pharmacophore is a description of the electronic characteristics necessary for interaction with a binding site. These characteristics may be representations of the ground and excited state wave functions of a pharmacophore, including specification of known expansions of such functions. Representations of a pharmacophore contain the chemical moieties, and/or atoms thereof, within the pharmacophore as well as their electronic characteristics and their three dimensional arrangement in space. Other representations may also be used because different chemical moieties may have similar characteristics. A non-limiting example is seen in the case of a -SH moiety at a particular position, which has similar characteristics to a -OH moiety at the same position. Chemical moieties that may be substituted for each other within a pharmacophore are referred to as "homologous".

[0027]   The present invention thus provides methods for producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of PAK6KD, said methods comprising introducing into a computer program a computer readable database comprising structural coordinates which may be used to produce a three dimensional representation of PAK6KD, determining a pharmacophore that fits within said binding pocket, computationally screening a plurality of compounds to determine which compound(s) or portion(s) thereof fit said pharmacophore, and storing a representation of said compound(s) or portion(s) thereof into a computer readable database. The database may be the same or different from that used to store the structural

coordinates of PAK6KD. Determination of a pharmacophore that fits may be performed by any means known in the art.

[0028]   With respect to c) the invention includes the computational screening of a plurality of chemical compounds to determine which compounds comprise a substructure that interacts with PAK6KD. The invention thus provides methods of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of PAK6KD, said methods comprising introducing into a computer program a computer readable database comprising structural coordinates which may be used to produce a three dimensional representation of PAK6KD, determining a chemical moiety that interacts with said binding pocket, computationally screening a plurality of compounds to determine which compound(s) comprise said moiety as a substructure of said compound(s), and storing a representation of said compound(s) and/or said moiety into a computer readable database which may be the same or different from that used to store the structural coordinates of PAK6KD.

[0029]   In one embodiment of the invention, the particulars of which may be used in combination with the other embodiments of the invention, a method is provided for producing structural information of a compound capable of binding PAK6KD by selecting at least one compound that potentially binds to PAK6KD. The method comprises constructing a three-dimensional structure of PAK6KD having structure coordinates selected from the group consisting of the structure coordinates of the crystals of the present invention, the structure coordinates of Fig. 4, and the structure coordinates of a protein having a root mean square deviation of the alpha carbon atoms of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å, when compared to the structure coordinates of Fig. 4, or a portion thereof, or constructing a three-dimensional structure of a molecule comprising a PAK6KD binding pocket or binding pocket homolog; and selecting at least one compound which potentially binds PAK6KD; wherein the selecting is performed with the aid of the constructed structure of PAK6KD.

[0030]   It is anticipated that in some cases, upon binding a compound, the conformation of the protein may be altered. Useful compounds may bind to this altered conformational form. Thus, included within the scope of the present invention are methods of producing structural information of a compound capable of binding PAK6KD by selecting compounds that potentially bind to a PAK6KD molecule or homolog where the molecule

or homolog comprises an amino acid sequence that is at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, and more preferably at least 90% identical to the amino acid sequence of Fig. 2, using, for example, a PSI BLAST search, such as, but not limited to version 2.2.2 (Altschul, S.F., et al., Nuc. Acids Rec. 25:3389-3402, 1997). Preferably at least 50%, more preferably at least 70% of the sequence is aligned in this analysis and where at least 50%, more preferably 60%, more preferably 70%, more preferably 80%, and most preferably 90% of the amino acids of the molecule or homolog have structure coordinates selected from the group consisting of the structure coordinates of the crystals of the present invention, the structure coordinates of Fig. 4, and the structure coordinates of a protein having a root mean square deviation of the alpha carbon atoms of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å, when compared to the structure coordinates of Fig. 4, or a portion thereof, or constructing a three dimensional structure of a molecule comprising a PAK6 binding pocket or binding pocket homolog; and selecting at least one compound which potentially binds PAK6; wherein the selecting is performed with the aid of the constructed structure. The selected compounds thus provide information concerning the structure of compounds that bind PAK6.

[0031]   Once produced, structural information of a compound capable of binding PAK6 may be stored in machine-readable form as described above for PAK6 structural information.

[0032]   In yet another aspect of the present invention, a method is provided of identifying a modulator of PAK6 by rational drug design, comprising; designing a potential modulator of PAK6 that forms covalent or non-covalent bonds with amino acids in a binding pocket of PAK6 based on the molecular structure coordinates of the crystals of the present invention, or based on the molecular structure coordinates of a molecule comprising a PAK6 binding pocket or binding pocket homolog; synthesizing the modulator; and determining whether the potential modulator affects the activity of PAK6. The binding pocket may, for example, comprise the active site of PAK6. The binding pocket may instead comprise an allosteric binding pocket of PAK6. A modulator may be, for example, an inhibitor, an activator, or an allosteric modulator of PAK6.

[0033]   Other methods of designing modulators of PAK6 include, for example, a method for identifying a modulator of PAK6 activity comprising: providing a computer

modeling program with a three dimensional conformation for a molecule that comprises a binding pocket of PAK6, or binding pocket homolog; providing a said computer modeling program with a set of structure coordinates of a chemical entity; using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket, or binding pocket homolog; and determining whether said chemical entity potentially binds to or interferes with said molecule; wherein binding to the molecule is indicative of potential modulation, including, for example, inhibition of PAK6 activity.

[0034] In another embodiment, a method is provided for designing a modulator of PAK6 activity comprising: providing a computer modeling program with a set of structure coordinates, or a three dimensional conformation derived therefrom, for a molecule that comprises a binding pocket of PAK6, or binding pocket homolog; providing a said computer modeling program with a set of structure coordinates, or a three dimensional conformation derived therefrom, of a chemical entity; using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket, or binding pocket homolog; computationally modifying the structure coordinates or three dimensional conformation of said chemical entity; and determining whether said modified chemical entity potentially binds to or interferes with said molecule; wherein binding to the molecule is indicative of potential modulation of PAK6 activity.

[0035] In other aspects, determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket, or binding pocket homolog, of the molecule or molecular complex; and computationally analyzing the results of the fitting operation to quantify the association between, or the interference with, the chemical entity and the binding pocket, or binding pocket homolog. In a further embodiment, the method further comprises screening a library of chemical entities.

[0036] The PAK6 modulator may also be designed *de novo*. Thus, the present invention also provides a method for designing a modulator of PAK6, comprising: providing a computer modeling program with a set of structure coordinates, or a three dimensional conformation derived therefrom, for a molecule that comprises a binding pocket having the structure coordinates of the binding pocket of PAK6, or a binding pocket homolog; computationally building a chemical entity represented by set of

structure coordinates; and determining whether the chemical entity is a modulator expected to bind to or interfere with the molecule wherein binding to the molecule is indicative of potential modulation of PAK6 activity. In other embodiments, determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex, or a binding pocket homolog; and computationally analyzing the results of the fitting operation to quantify the association between, or the interference with, the chemical entity and the binding pocket, or a binding pocket homolog.

[0037]   In yet other embodiments, once a modulator is computationally designed or identified, the potential modulator may be supplied or synthesized, then assayed to determine whether it inhibits PAK6 activity. The molecular structure coordinates and/or machine-readable media associated with the PAK6 structure and/or a compound capable of binding PAK6KD may be used in the production of compounds capable of binding PAK6. Methods for the production of such compounds include the preparation of an initial compound containing chemical groups most likely to bind or interact with residues of PAK6KD based upon the molecular structure coordinates of PAK6KD and/or a compound capable of binding it. Such an initial compound may also be viewed as a scaffold comprising one or more reactive moieties (chemical groups) that are capable of binding or interacting with PAK6 residues. The initial compound may be further optimized for binding to PAK6 by introduction of additional chemical groups for increased interactions with PAK6KD residues. An initial compound may thus comprise reactive groups which may be used to introduce one or more additional chemical groups into the compound. The introduction of additional groups may also be at positions of an initial compound that do not result in interactions with PAK6 residues, but rather improve other characteristics of the compound, such as, but not limited to, stability against degradation, handling or storage, solubility in hydrophilic and hydrophobic environments, and overall charge dynamics of the compound.

[0038]   The present invention also provides modulators of PAK6 activity identified, designed, or made according to any of the methods of the present invention, as well as pharmaceutical compositions comprising such modulators. Pharmaceutical compositions may be in the form of a salt, and may further comprise a pharmaceutically acceptable carrier. A modulator may be identified or confirmed as an activator or inhibitor by contacting a protein that comprises a PAK6 active site or binding pocket with said

modulator and determining whether it activates or inhibits the activity of the protein. The activity may be PAK6 activity. A naturally occurring PAK6 protein may also be used in such methods.

[0039]   Also provided in the present invention is a method of modulating PAK6 activity comprising contacting PAK6 with a modulator designed or identified according to the present invention. Methods include methods of treating a disease or condition associated with inappropriate PAK6 activity comprising the method of administering by, for example, contacting cells of an individual with a PAK6 modulator designed or identified according to the present invention. The term "inappropriate activity" refers to PAK6 activity that is higher or lower than that in normal cells.

[0040]   The molecular structure coordinates and/or machine-readable media of the invention may also be used in identification of active sites and binding pockets of PAK6KD. Methods for the identification of such sites and pockets are known in the art. The techniques include the use of sequence comparisons to identify regions of homology or conserved substitutions which define conserved structure among different forms of PAK6KD. The techniques may also include comparisons of structure with other proteins with the same activities as PAK6 to identify the structural components (e.g. amino acid residues and/or their arrangement in three dimensions) of the active sites and binding pockets.

[0041]   In another embodiment of the present invention, a method is provided for producing a mutant of PAK6, having an altered property relative to PAK6, comprising, a) constructing a three-dimensional structure of PAK6KD having structure coordinates selected from the group consisting of the structure coordinates of the crystals of the present invention, the structure coordinates of Fig. 4, and the structure coordinates of a protein having a root mean square deviation of the alpha carbon atoms of the protein of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å, when compared to the structure coordinates of Fig. 4; b) using modeling methods to identify in the three-dimensional structure at least one structural part of the PAK6KD molecule wherein an alteration in the structural part is predicted to result in the altered property; c) providing a nucleic acid molecule having a modified sequence that encodes a deletion, insertion, or substitution of one or more amino acids at a position corresponding to the structural part; and d) expressing the nucleic acid molecule to produce the mutant; wherein

the mutant has at least one altered property relative to the parent. The mutant may, for example, have altered PAK6 activity. The altered PAK6 activity may be, for example, altered binding activity, altered enzymatic activity, and altered immunogenicity, such as, for example, where an epitope of the protein is altered because of the mutation. The mutation that alters the epitope may be, for example, within the region of the protein that comprises the epitope. Or, the mutation may be, for example, at a site outside of the epitope region, yet causes a conformational change in the epitope region. Those of ordinary skill in the art will recognize that the region that contains the epitope may comprise either contiguous or non-contiguous amino acids.

[0042]   Also provided in the present invention is a method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising: crystallizing the molecule or molecular complex; generating an x-ray diffraction pattern from the crystallized molecule or molecular complex; and using a molecular replacement method to interpret the structure of said molecule; wherein said molecular replacement method uses the structure coordinates of Fig. 4, or structure coordinates having a root mean square deviation for the alpha-carbon atoms of said structure coordinates of up to about 2.0Å, preferably up to about 1.75Å, preferably up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1.0Å, preferably up to about 0.75Å, the structure coordinates of the binding pocket of Fig. 4, or a binding pocket homolog. The coordinates of the resulting structure are stored in a computer readable database as described herein.

[0043]   In another aspect of the invention, a method is provided of using the PAK6KD structure coordinates, or the PAK6KD binding site, active site, or accessory binding site structure coordinates as an anti-target in rational drug design. When designing compounds that modulate a protein target's activity, it is often desirable to increase specificity for the target and reduce side effects. The protein structure information is useful to design compounds that do not bind to, interact with, or modulate the activity of the protein. Thus, one aspect of the present invention comprises the use of anti-target structures to assist in selecting a compound that modulates the target, but does not modulate PAK6, or does not modulate PAK6 in sufficient amount to cause a detrimental side affect. The target may, for example, be another kinase. The target may be another PAK kinase.

[0044]   Thus, in one aspect of the invention, a method is provided of identifying a compound that modulates the activity of a target protein, comprising: a) introducing into a computer program information derived from structural coordinates defining an active site

conformation of a target protein molecule based upon three-dimensional structure determination, wherein said program utilizes or displays the three-dimensional structure thereof; b) generating a three-dimensional representation of the active site cavity of said target protein in said computer program; c) superimposing a model of a test compound on the model of said active site of said target protein; d) assessing whether said test compound model fits spatially into the active site of said target protein; e) generating a three-dimensional representation of a binding pocket of a PAK6KD protein in a computer program; f) superimposing a model of said test compound on the model of said binding pocket of said PAK6KD protein; and g) assessing whether said test compound model fits spatially into said binding pocket of said PAK6KD protein.

[0045]　The binding pocket of the PAK6KD protein may be, for example, an active site or an accessory binding site. Said target protein may be a kinase. The test compound model may or may not fit spatially into the binding pocket of said PAK6KD protein. The method may further comprise performing a fitting operation to computationally analyze the association between the test compound and the PAK6KD protein. The test compound may bind with greater efficiency to the target protein than to the PAK6KD protein; the test compound likely does not bind to the PAK6KD protein.

[0046]　In yet another aspect of the invention, a method is provided for homology modeling of a PAK6KD homolog comprising: aligning the amino acid sequence of a PAK6KD homolog with an amino acid sequence of PAK6KD; incorporating the sequence of the PAK6KD homolog into a model of the structure of PAK6KD, wherein said model has the same structure coordinates as the structure coordinates of Fig. 4, or wherein the structure coordinates of said model's alpha-carbon atoms have a root mean square deviation from the structure coordinates of Fig. 4 of up to about 2.0Å, preferably up to about 1.75Å, preferably up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1.0Å, and preferably up to about 0.75Å, to yield a preliminary model of said homolog; subjecting the preliminary model to energy minimization to yield an energy minimized model; and remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of said homolog.

[0047]　The invention also provides PAK6KD in crystalline form, as well as a computer or machine readable medium containing information that reflects the three dimensional structure of such crystals and/or compounds that interact with them. Also provided is a method of producing a computer readable database containing the three-dimensional

molecular structure coordinates of a compound capable of binding the active site or binding pocket of a PAK6KD but not another protein molecule. Such a method comprises a) introducing into a computer program information concerning the structure of PAK6KD; b) generating a three-dimensional representation of the active site or binding pocket of PAK6KD in said computer program; c) superimposing a three-dimensional model of at least one binding test compound on said representation of the active site or binding pocket; d) assessing whether said test compound model fits spatially into the active site or binding pocket of PAK6KD; e) assessing whether a compound that fits will fit a three-dimensional model of another protein, the structural coordinates of which are also introduced into said computer program and used to generate a three-dimensional representation of the other protein; and f) storing the three-dimensional molecular structure coordinates of a model that does not fit the other protein into a computer readable database. An alternative form of such a method produces a computer readable database containing the three-dimensional molecular structural coordinates of a compound capable of specifically binding the active site or binding pocket of PAK6KD, said method comprising introducing into a computer program a computer readable database containing the structural coordinates of PAK6KD, generating a three-dimensional representation of the active site or binding pocket of PAK6KD in said computer program, superimposing a three-dimensional model of at least one binding test compound on said representation of the active site or binding pocket, assessing whether said test compound model fits spatially into the active site or binding pocket of PAK6KD, assessing whether a compound that fits will fit a three-dimensional model of another protein, the structural coordinates of which are also introduced into said computer program and used to generate a three-dimensional representation of the other protein, and storing the three-dimensional molecular structural coordinates of a model that does not fit the other protein into a computer readable database. Conversely, such methods may be used to determine that compounds identified as binding other proteins do not bind PAK6KD. Thus, such methods may use PAK6KD as an anti-target, to identify compounds that do not bind PAK6KD.

[0048]   The invention also provides methods comprising the production of a co-crystal of a compound and PAK6KD. Such co-crystals may be used in a variety of ways, including the determination of structural coordinates of the compound and/or PAK6KD, or a binding pocket thereof, in the co-crystal. Such coordinates may be introduced and/or stored in a computer readable database in accordance with the present invention for further

use. The invention thus provides methods of producing a computer readable database comprising a representation of a binding pocket of PAK6KD in a co-crystal with a compound, said methods comprising preparing a binding test compound represented in a computer readable database produced by any method described herein, forming a co-crystal of said compound with a protein comprising a binding pocket of PAK6KD, obtaining the structural coordinates of said binding pocket in said co-crystal, and introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database. The invention further provides for a combination of such methods with rational compound design by providing methods of producing a computer readable database comprising a representation of a binding pocket of PAK6KD in a co-crystal with a compound rationally designed to be capable of binding said binding pocket, said methods comprising preparing a binding test compound represented in a computer readable database produced by any method described herein, forming a co-crystal of said compound with a protein comprising a binding pocket of PAK6KD, obtaining the structural coordinates of said binding pocket in said co-crystal, and introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database.

[0049] The invention is illustrated by way of the present application, including working examples demonstrating the purification and the crystallization of PAK6KD, the characterization of crystals, the collection of diffraction data, and the determination and analysis of the three-dimensional structure of PAK6KD.

BRIEF DESCRIPTION OF THE FIGURES

[0050] FIG. 1 provides a ribbon diagram of the structure of PAK6KD.

[0051] FIG. 2 provides the predicted amino acid sequence of the PAK6KD expressed protein used to obtain the crystals and structural coordinates of the present invention. Note that this amino acid sequence may comprise amino acids encoded by the ORF, as well as other amino acids encoded by the expression vector. Further information regarding sequence changes, if any, may be found in the examples.

[0052] FIG. 3 provides a ribbon diagram of the structure of PAK6KD.

[0053] FIG. 4 (A-RR) provides the molecular structure coordinates of PAK6KD.

[0054] The following abbreviations are used in Figure 4.

[0055] "Atom Type" and "Atom" refer to the individual atom whose coordinates are provided, with and without indicating the position of the atom in the amino acid residue, respectively. The first letter in the column refers to the element.

[0056] HETATM refers to atomic coordinates within non-standard HET groups, such as prosthetic groups, inhibitors, solvent molecules, and ions for which coordinates are supplied. HETATMS include residues that are a) not one of the standard amino acids, including, for example, SeMet and SeCys, b) not one of the nucleic acids (C, G, A, T, U, and I), c) not one of the modified versions of nucleic acids (+C, +G, +A, +T, +U, and +I), and d) not an unknown amino acid or nucleic acid where UNK is used to indicate the unknown residue name.

[0057] "Residue" refers to the amino acid residue.

[0058] "#" refers to the residue number, starting from the N-terminal amino acid. The number designations of each amino acid residues reflect the position predicted in the expressed protein, including the His tag and the initial methionine.

[0059] "X, Y and Z" provide the Cartesian coordinates of the atom.

[0060] "B" is a thermal factor that measures movement of the atom around its atomic center.

[0061] "OCC" refers to occupancy, and represents the percentage of time the atom type occupies the particular coordinate. OCC values range from 0 to 1, with 1 being 100%.

[0062] Structure coordinates for PAK6KD according to Figure 4 may be modified by mathematical manipulation. Such manipulations include, but are not limited to, crystallographic permutations of the raw structure coordinates, fractionalization of the raw structure coordinates, integer additions or subtractions to sets of the raw structure coordinates, inversion of the raw structure coordinates, and any combination of the above.

Abbreviations

[0063] The amino acid notations used herein for the twenty genetically encoded amino acids are:

Amino Acid	One-Letter Symbol	Three-Letter Symbol
Alanine	A	Ala
Arginine	R	Arg

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Asparagine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamine	Q	Gln
Glutamic acid	E	Glu
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val

[0064] As used herein, unless specifically delineated otherwise, the three-letter amino acid abbreviations designate amino acids in the L-configuration. Amino acids in the D-configuration are preceded with a "D-." For example, Arg designates L-arginine and D-Arg designates D-arginine. Likewise, the capital one-letter abbreviations refer to amino acids in the L-configuration. Lower-case one-letter abbreviations designate amino acids in the D-configuration. For example, "R" designates L-arginine and "r" designates D-arginine.

[0065] Unless noted otherwise, when polypeptide sequences are presented as a series of one-letter and/or three-letter abbreviations, the sequences are presented in the N→C direction, in accordance with common practice.

Definitions

[0066] As used herein, the following terms shall have the following meanings:

[0067] "Genetically Encoded Amino Acid" refers to the twenty amino acids that are defined by genetic codons. The genetically encoded amino acids are glycine and the L-isomers of alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, arginine and lysine.

[0068] "Non-Genetically Encoded Amino Acid" refers to amino acids that are not defined by genetic codons. Non-genetically encoded amino acids include derivatives or analogs of the genetically-encoded amino acids that are capable of being enzymatically incorporated into nascent polypeptides using conventional expression systems, such as selenomethionine (SeMet) and selenocysteine (SeCys); isomers of the genetically-encoded amino acids that are not capable of being enzymatically incorporated into nascent polypeptides using conventional expression systems, such as D-isomers of the genetically-encoded amino acids; L- and D-isomers of naturally occurring α-amino acids that are not defined by genetic codons, such as α-aminoisobutyric acid (Aib); L- and D-isomers of synthetic α-amino acids that are not defined by genetic codons; and other amino acids such as β-amino acids, γ-amino acids, etc. In addition to the D-isomers of the genetically-encoded amino acids, common non-genetically encoded amino acids include, but are not limited to norleucine (Nle), penicillamine (Pen), N-methylvaline (MeVal), homocysteine (hCys), homoserine (hSer), 2,3-diaminobutyric acid (Dab) and ornithine (Orn). Additional exemplary non-genetically encoded amino acids are found, for example, in *Practical Handbook of Biochemistry and Molecular Biology*, Fasman, Ed., CRC Press, Inc., Boca Raton, FL, pp. 3-76, 1989, and the various references cited therein.

[0069] "Hydrophilic Amino Acid" refers to an amino acid having a side chain exhibiting a hydrophobicity of up to about zero according to the normalized consensus hydrophobicity scale of Eisenberg *et al.*, J. Mol. Biol. 179:125-42, 1984. Genetically encoded hydrophilic amino acids include Thr (T), Ser (S), His (H), Glu (E), Asn (N), Gln (Q), Asp (D), Lys (K) and Arg (R). Non-genetically encoded hydrophilic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, ornithine (Orn), 2,3-diaminobutyric acid (Dab) and homoserine (hSer).

[0070] "Acidic Amino Acid" refers to a hydrophilic amino acid having a side chain pK value of up to about 7 under physiological conditions. Acidic amino acids typically have negatively charged side chains at physiological pH due to loss of a hydrogen ion.

Genetically encoded acidic amino acids include Glu (E) and Asp (D). Non-genetically encoded acidic amino acids include D-Glu (e) and D-Asp (d).

[0071]   "Basic Amino Acid" refers to a hydrophilic amino acid having a side chain pK value of greater than 7 under physiological conditions. Basic amino acids typically have positively charged side chains at physiological pH due to association with hydronium ion. Genetically encoded basic amino acids include His (H), Arg (R) and Lys (K). Non-genetically encoded basic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, ornithine (Orn) and 2,3-diaminobutyric acid (Dab).

[0072]   "Polar Amino Acid" refers to a hydrophilic amino acid having a side chain that is uncharged at physiological pH, but which comprises at least one covalent bond in which the pair of electrons shared in common by two atoms is held more closely by one of the atoms. Genetically encoded polar amino acids include Asn (N), Gln (Q), Ser (S), and Thr (T). Non-genetically encoded polar amino acids include the D-isomers of the above-listed genetically-encoded amino acids and homoserine (hSer).

[0073]   "Hydrophobic Amino Acid" refers to an amino acid having a side chain exhibiting a hydrophobicity of greater than zero according to the normalized consensus hydrophobicity scale of Eisenberg *et al.*, J. Mol. Biol. 179:125-42, 1984. Genetically encoded hydrophobic amino acids include Pro (P), Ile (I), Phe (F), Val (V), Leu (L), Trp (W), Met (M), Ala (A), Gly (G) and Tyr (Y). Non-genetically encoded hydrophobic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, norleucine (Nle) and N-methyl valine (MeVal).

[0074]   "Aromatic Amino Acid" refers to a hydrophobic amino acid having a side chain comprising at least one aromatic or heteroaromatic ring. The aromatic or heteroaromatic ring may contain one or more substituents such as -OH, -SH, -CN, -F, -Cl, -Br, -I, $-NO_2$, -NO, $-NH_2$, -NHR, -NRR, -C(O)R, -C(O)OH, -C(O)OR, $-C(O)NH_2$, -C(O)NHR, -C(O)NRR and the like where each R is independently (C_1-C_6) alkyl, (C_1-C_6) alkenyl, or (C_1-C_6) alkynyl. Genetically encoded aromatic amino acids include Phe (F), Tyr (Y), Trp (W) and His (H). Non-genetically encoded aromatic amino acids include the D-isomers of the above-listed genetically-encoded amino acids.

[0075]   "Apolar Amino Acid" refers to a hydrophobic amino acid having a side chain that is uncharged at physiological pH and which has bonds in which the pair of electrons shared in common by two atoms is generally held equally by each of the two atoms (*i.e.*, the side chain is not polar). Genetically encoded apolar amino acids include Leu (L), Val

(V), Ile (I), Met (M), Gly (G) and Ala (A). Non-genetically encoded apolar amino acids include the D-isomers of the above-listed genetically-encoded amino acids, norleucine (Nle) and N-methyl valine (MeVal).

[0076] "Aliphatic Amino Acid" refers to a hydrophobic amino acid having an aliphatic hydrocarbon side chain. Genetically encoded aliphatic amino acids include Ala (A), Val (V), Leu (L) and Ile (I). Non-genetically encoded aliphatic amino acids include the D-isomers of the above-listed genetically-encoded amino acids, norleucine (Nle) and N-methyl valine (MeVal).

[0077] "Helix-Breaking Amino Acid" refers to those amino acids that have a propensity to disrupt the structure of α-helices when contained at internal positions within the helix. Amino acid residues exhibiting helix-breaking properties are well-known in the art (see, e.g., Chou & Fasman, Ann. Rev. Biochem. 47:251-76, 1978) and include Pro (P), D-Pro (p), Gly (G) and potentially all D-amino acids (when contained in an L-polypeptide; conversely, L-amino acids disrupt helical structure when contained in a D-polypeptide).

[0078] "Cysteine-like Amino Acid" refers to an amino acid having a side chain capable of participating in a disulfide linkage. Thus, cysteine-like amino acids generally have a side chain containing at least one thiol (-SH) group. Cysteine-like amino acids are unusual in that they can form disulfide bridges with other cysteine-like amino acids. The ability of Cys (C) residues and other cysteine-like amino acids to exist in a polypeptide in either the reduced free -SH or oxidized disulfide-bridged form affects whether they contribute net hydrophobic or hydrophilic character to a polypeptide. Thus, while Cys (C) exhibits a hydrophobicity of 0.29 according to the consensus scale of Eisenberg (Eisenberg, 1984, supra), it is to be understood that for purposes of the present invention Cys (C) is categorized as a polar hydrophilic amino acid, notwithstanding the general classifications defined above. Other cysteine-like amino acids are similarly categorized as polar hydrophilic amino acids. Typical cysteine-like residues include, for example, penicillamine (Pen), homocysteine (hCys), etc.

[0079] As will be appreciated by those of skill in the art, the above-defined classes or categories are not mutually exclusive. Thus, amino acids having side chains exhibiting two or more physical-chemical properties may be included in multiple categories. For example, amino acid side chains having aromatic groups that are further substituted with polar substituents, such as Tyr (Y), may exhibit both aromatic hydrophobic properties and polar or hydrophilic properties, and could therefore be included in both the aromatic and

polar categories. Typically, amino acids will be categorized in the class or classes that most closely define their net physical-chemical properties. The appropriate categorization of any amino acid will be apparent to those of skill in the art.

[0080] Other amino acid residues not specifically mentioned herein may be readily categorized based on their observed physical and chemical properties in light of the definitions provided herein.

[0081] "Wild-type PAK6KD" refers to a polypeptide having an amino acid sequence that corresponds to the amino acid sequence of a naturally-occurring PAK6KD, and wherein said polypeptide, when compared to PAK6KD, has an rmsd of its backbone atoms of less than 2Å.

[0082] "Homo sapiens PAK6KD" refers to a polypeptide having an amino acid sequence that corresponds identically to the wild-type PAK6KD from Homo sapiens.

[0083] By "or" is meant one, or another member of a group, or more than one member. For example, A, B, or C, may indicate any of the following: A alone; B alone; C alone; A and B; B and C; A and C; A, B, and C.

[0084] "Association" refers to the status of two or more molecules that are in close proximity to each other. The two molecules may be associated non-covalently, for example, by hydrogen-bonding, van der Waals, electrostatic or hydrophobic interactions, or covalently.

[0085] "Co-Complex" refers to a polypeptide in association with one or more compounds. The association may be, for example, covalent or non-covalent. A "PAK6KD co-complex" refers to PAK6KD, or a functional subunit or fragment thereof, in association with one or more compounds. Such compounds include, by way of example and not limitation, cofactors, ligands, substrates, substrate analogues, inhibitors, allosteric affecters, etc. Lead compounds for designing PAK6 inhibitors include, but are not restricted to, ATP; β-amido ATP; AMP-PNP, staurosporine, and derivatives and analogs thereof. A co-complex may also refer to a computer represented, or *in silica* generated association between a peptide and a compound. An "unliganded" form of a protein structure, or structural coordinates thereof, refers to the coordinates of the native form of a protein structure, or the apostructure, not a co-complex. A "liganded" form refers to the coordinates of a protein or peptide that is part of a co-complex. Unliganded forms include peptides and proteins associated with various ions, such as manganese, zinc, and magnesium, as well as with water. Ligands include natural substrates, non-natural

substrates, inhibitors, substrate analogs, agonists or antagonists, proteins, co-factors small molecules, test compounds, and fragments of test compounds, as well as, optionally, in addition, various ions or water.

[0086]   "Mutant" refers to a polypeptide characterized by an amino acid sequence that differs from the wild-type sequence by the substitution of at least one amino acid residue of the wild-type sequence with a different amino acid residue and/or by the addition and/or deletion of one or more amino acid residues to or from the wild-type sequence. The additions and/or deletions may be from an internal region of the wild-type sequence and/or at either or both of the N- or C-termini. A mutant polypeptide may have substantially the same three-dimensional structure as the corresponding wild-type polypeptide. A mutant may have, but need not have, PAK6 activity. A mutant may display biological activity that is substantially similar to that of the wild-type PAK6KD. By "substantially similar biological activity" is meant that the mutant displays biological activity that is within 1% to 10,000% of the biological activity of the wild-type polypeptide, for example, within 25% to 5,000%, and, for example, within 50% to 500%, or 75% to 200% of the biological activity of the wild-type polypeptide, using assays known to those of ordinary skill in the art for that particular class of polypeptides. Mutants may also decrease or eliminate PAK6KD activity. Mutants may be synthesized according to any method known to those skilled in the art, including, but not limited to, those methods of expressing PAK6KD molecules described herein.

[0087]   "Active Site" refers to a site in PAK6KD that associates with the substrate for PAK6 activity. This site may include, for example, residues involved in catalysis, as well as residues involved in binding a substrate. Inibitors may bind to the residues of the active site. In PAK6KD, the active site includes one or more of the following amino acid residues: Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

[0088]   Preferably, the active site comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544, preferably the active site further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530. Preferably the active site further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 .

Amino acid residue numbers presented herein refer to the sequence of wild type full length PAK6. Those of ordinary skill in the art may easily determine the residue numbers corresponding to any modified form of PAK6 using standard alignment protocols, including, for example, alignments done by hand.

[0089] "Binding Pocket" refers to a region in PAK6 which associates with a ligand such as a natural substrate, non-natural substrate, inhibitor, substrate analog, agonist or antagonist, protein, co-factor or small molecule, as well as, optionally, in addition, various ions or water, and/or has an internal cavity sufficient to bind a small molecule and may be used as a target for binding drugs. The term includes the active site but is not limited thereby.

[0090] "Accessory Binding Pocket" refers to a binding pocket in PAK6KD other than that of the "active site."

[0091] "Conservative Mutant" refers to a mutant in which at least one amino acid residue from the wild-type sequence is substituted with a different amino acid residue that has similar physical and chemical properties, $i.e.$, an amino acid residue that is a member of the same class or category, as defined above. For example, a conservative mutant may be a polypeptide that differs in amino acid sequence from the wild-type sequence by the substitution of a specific aromatic Phe (F) residue with an aromatic Tyr (Y) or Trp (W) residue.

[0092] "Non-Conservative Mutant" refers to a mutant in which at least one amino acid residue from the wild-type sequence is substituted with a different amino acid residue that has dissimilar physical and/or chemical properties, $i.e.$, an amino acid residue that is a member of a different class or category, as defined above. For example, a non-conservative mutant may be a polypeptide that differs in amino acid sequence from the wild-type sequence by the substitution of an acidic Glu (E) residue with a basic Arg (R), Lys (K) or Orn residue.

[0093] "Deletion Mutant" refers to a mutant having an amino acid sequence that differs from the wild-type sequence by the deletion of one or more amino acid residues from the wild-type sequence. The residues may be deleted from internal regions of the wild-type sequence and/or from one or both termini.

[0094] "Truncated Mutant" refers to a deletion mutant in which the deleted residues are from the N- and/or C-terminus of the wild-type sequence.

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[0095]   "Extended Mutant" refers to a mutant in which additional residues are added to the N- and/or C-terminus of the wild-type sequence.

[0096]   "Methionine mutant" refers to (1) a mutant in which at least one methionine residue of the wild-type sequence is replaced with another residue, such as with an aliphatic residue, such as an Ala (A), Leu (L), or Ile (I) residue; or (2) a mutant in which a non-methionine residue, such as an aliphatic residue, such as an Ala (A), Leu (L) or Ile (I) residue, of the wild-type sequence is replaced with a methionine residue.

[0097]   "Selenomethionine mutant" refers to (1) a mutant which includes at least one selenomethionine (SeMet) residue, typically by substitution of a Met residue of the wild-type sequence with a SeMet residue, or by addition of one or more SeMet residues at one or both termini, or (2) a methionine mutant in which at least one Met residue is substituted with a SeMet residue. In some embodiments, each Met residue is substituted with a SeMet residue.

[0098]   "Cysteine mutant" refers to a mutant in which at least one cysteine residue of the wild-type sequence is replaced with another residue, such as with a Ser (S) residue.

[0100]   "Serine mutant" refers to a mutant in which at least one serine residue of the wild-type sequence is replaced with another residue, such as with a cysteine residue.

[0101]   "Selenocysteine mutant" refers to (1) a mutant which includes at least one selenocysteine (SeCys) residue, typically by substitution of a Cys residue of the wild-type sequence with a SeCys residue, or by addition of one or more SeCys residues at one or both termini, or (2) a cysteine mutant in which at least one Cys residue is substituted with a SeCys residue. In some embodiments, SeCys mutants are those in which each Cys residue is substituted with a SeCys residue.

[0102]   "Homolog" refers to a polypeptide having at least 30%, preferably at least 40%, preferably at least 50%, preferably at least 60%, preferably at least 70%, more preferably at least 80%, and most preferably at least 90% amino acid sequence identity or having a BLAST E-value of 1×10^{-6} over at least 100 amino acids (Altschul et al., *Nucleic Acids Res.*, 25:3389-402, 1997) with PAK6KD or any functional domain of PAK6KD.

[0103]   "Crystal" refers to a composition comprising a polypeptide in crystalline form. The term "crystal" includes native crystals, heavy-atom derivative crystals and co-crystals, as defined herein.

[0104]   "Native Crystal" refers to a crystal wherein the polypeptide is substantially pure. As used herein, native crystals do not include crystals of polypeptides comprising amino

acids that are modified with heavy atoms, such as crystals of selenomethionine mutants, selenocysteine mutants, etc.

[0105] "Heavy-atom Derivative Crystal" refers to a crystal wherein the polypeptide is in association with one or more heavy-metal atoms. As used herein, heavy-atom derivative crystals include native crystals into which a heavy metal atom is soaked, as well as crystals of selenomethionine mutants and selenocysteine mutants.

[0106] "Co-Crystal" refers to a crystalline form of a co-complex.

[0107] "Apo-crystal" refers to a crystal wherein the polypeptide is substantially pure and substantially free of compounds that might form a co-complex with the polypeptide such as cofactors, ligands, substrates, substrate analogues, inhibitors, allosteric affecters, etc.

[0108] "Diffraction Quality Crystal" refers to a crystal that is well-ordered and of a sufficient size, *i.e.*, at least 10μm, at least 50μm, or at least 100μm in its smallest dimension such that it produces measurable diffraction to at least 3Å resolution, preferably to at least 2Å resolution, and most preferably to at least 1.5Å resolution or lower. Diffraction quality crystals include native crystals, heavy-atom derivative crystals, and co-crystals.

[0109] "Unit Cell" refers to the smallest and simplest volume element (*i.e.*, parallelepiped-shaped block) of a crystal that is completely representative of the unit or pattern of the crystal, such that the entire crystal may be generated by translation of the unit cell. The dimensions of the unit cell are defined by six numbers: dimensions a, b and c and the angles are defined as α, β, and γ (Blundell *et al.*, Protein Crystallography, 83-84, Academic Press. 1976). A crystal is an efficiently packed array of many unit cells.

[0110] "Triclinic Unit Cell" refers to a unit cell in which a≠b≠c and α≠β≠γ.

[0111] "Monoclinic Unit Cell" refers to a unit cell in which a≠b≠c; α=γ=90°; and β>90°.

[0112] "Hexagonal Unit Cell" refers to a unit cell in which a=b≠c; α=β= 90°; and γ=120°.

[0113] "Orthorhombic Unit Cell" refers to a unit cell in which a≠b≠c; and α=β = γ=90°.

[0114] "Tetragonal Unit Cell" refers to a unit cell in which a=b≠c; and α =β =γ =90°.

[0115] "Trigonal/Rhombohedral Unit Cell" refers to a unit cell in which a=b=c; and $\alpha=\beta=\gamma \neq 90°$.

[0116] "Trigonal/Hexagonal Unit Cell" refers to a unit cell in which a=b≠c; $\alpha=\beta=90°$; and $\gamma=120°$.

[0117] "Cubic Unit Cell" refers to a unit cell in which a=b=c; and $\alpha=\beta=\gamma=90°$.

[0118] "Crystal Lattice" refers to the array of points defined by the vertices of packed unit cells.

[0119] "Space Group" refers to the set of symmetry operations of a unit cell. In a space group designation (e.g., C2) the capital letter indicates the lattice type and the other symbols represent symmetry operations that may be carried out on the unit cell without changing its appearance.

[0120] "Asymmetric Unit" refers to the largest aggregate of molecules in the unit cell that possesses no symmetry elements that are part of the space group symmetry, but that may be juxtaposed on other identical entities by symmetry operations.

[0121] "Crystallographically-Related Dimer (or oligomer)" refers to a dimer (or oligomer, such as, for example, a trimer or a tetramer) of two (or more) molecules wherein the symmetry axes or planes that relate the two (or more) molecules comprising the dimer (or oligomer) coincide with the symmetry axes or planes of the crystal lattice.

[0122] "Non-Crystallographically-Related Dimer (or oligomer)" refers to a dimer (or oligomer, such as, for example, a trimer or a tetramer) of two (or more) molecules wherein the symmetry axes or planes that relate the two (or more) molecules comprising the dimer (or oligomer) do not coincide with the symmetry axes or planes of the crystal lattice.

[0123] "Isomorphous Replacement" refers to the method of using heavy-atom derivative crystals to obtain the phase information necessary to elucidate the three-dimensional structure of a crystallized polypeptide (Blundell et al., Protein Crystallography, Academic Press, esp. pp. 151-64, 1976; Methods in Enzymology 276:361-557, Academic Press, 1997). The phrase "heavy-atom derivatization" is synonymous with "isomorphous replacement."

[0124] "Multi-Wavelength Anomalous Dispersion or MAD" refers to a crystallographic technique in which X-ray diffraction data are collected at several different wavelengths from a single heavy-atom derivative crystal, wherein the heavy atom has absorption edges near the energy of incoming X-ray radiation. The resonance between X-

rays and electron orbitals leads to differences in X-ray scattering from absorption of the X-rays (known as anomalous scattering) and permits the locations of the heavy atoms to be identified, which in turn provides phase information for a crystal of a polypeptide. A detailed discussion of MAD analysis may be found in Hendrickson, Trans. Am. Crystallogr. Assoc., 21:11, 1985; Hendrickson *et al.*, EMBO J. 9:1665, 1990; and Hendrickson, Science, 254:51-58, 1991.

[0125]   "Single Wavelength Anomalous Dispersion or SAD" refers to a crystallographic technique in which X-ray diffraction data are collected at a single wavelength from a single native or heavy-atom derivative crystal, and phase information is extracted using anomalous scattering information from atoms such as sulfur or chlorine in the native crystal or from the heavy atoms in the heavy-atom derivative crystal. The wavelength of X-rays used to collect data for this phasing technique needs to be close to the absorption edge of the anomalous scatterer. A detailed discussion of SAD analysis may be found in Brodersen, et al., Acta Cryst., D56:431-41, 2000.

[0126]   "Single Isomorphous Replacement With Anomalous Scattering or SIRAS" refers to a crystallographic technique that combines isomorphous replacement and anomalous scattering techniques to provide phase information for a crystal of a polypeptide. X-ray diffraction data are collected at a single wavelength, usually from a single heavy-atom derivative crystal. Phase information obtained only from the location of the heavy atoms in a single heavy-atom derivative crystal leads to an ambiguity in the phase angle, which is resolved using anomalous scattering from the heavy atoms. Phase information is therefore extracted from both the location of the heavy atoms and from anomalous scattering of the heavy atoms. A detailed discussion of SIRAS analysis may be found in North, Acta Cryst. 18:212-16, 1965; Matthews, Acta Cryst., 20:82-86, 1966.

[0127]   "Molecular Replacement" refers to the method using the structure coordinates of a known polypeptide to calculate initial phases for a new crystal of a polypeptide whose structure coordinates are unknown. This is done by orienting and positioning a polypeptide whose structure coordinates are known within the unit cell of the new crystal. Phases are then calculated from the oriented and positioned polypeptide and combined with observed amplitudes to provide an approximate Fourier synthesis of the structure of the polypeptides comprising the new crystal. The model is then refined to provide a refined set of structure coordinates for the new crystal (Lattman, Methods in Enzymology, 115:55-77, 1985; Rossmann, "The Molecular Replacement Method," Int. Sci. Rev. Ser.

No. 13, Gordon & Breach, New York, 1972; Methods in Enzymology, Vols. 276, 277 (Academic Press, San Diego 1997)). Molecular replacement may be used, for example, to determine the structure coordinates of a crystalline mutant or homolog of PAK6KD using the structure coordinates of PAK6KD.

[0128]   "Structure coordinates" refers to mathematical coordinates derived from mathematical equations related to the patterns obtained on diffraction of a monochromatic beam of X-rays by the atoms (scattering centers) of a PAK6KD in crystal form. The diffraction data are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are used to establish the positions of the individual atoms within the unit cell of the crystal.

[0129]   "Having substantially the same three-dimensional structure" refers to a polypeptide that is characterized by a set of molecular structure coordinates that have a root mean square deviation (r.m.s.d.) of up to about or equal to 1.5Å, preferably 1.25Å, preferably 1Å, and preferably 0.5Å, and preferably 0.25Å, when superimposed onto the molecular structure coordinates of Fig. 4 when at least 50% to 100% of the C-alpha atoms of the coordinates are included in the superposition. The program MOE may be used to compare two structures (Chemical Computing Group, Inc., Montreal, Canada). Where structure coordinates are not available for a particular amino acid residue(s), those coordinates are not included in the calculation.

[0130]   "α-C" or "α-carbon" or "CA" as used herein, "α-C" or "α-carbon" refer to the alpha carbon of an amino acid residue.

[0131]   "α-helix" refers to the conformation of a polypeptide chain in the form of a spiral chain of amino acids stabilized by hydrogen bonds.

[0132]   The term "β-sheet" refers to the conformation of a polypeptide chain stretched into an extended zig-zag conformation. Portions of polypeptide chains that run "parallel" all run in the same direction. Where polypeptide chains are "antiparallel," neighboring chains run in opposite directions from each other. The term "run" refers to the N to COOH direction of the polypeptide chain.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline PAK6

[0133] Both native and heavy-atom derivative crystals, such as those obtained from selenium methionine derivative PAK6KD may be used to obtain the molecular structure coordinates of the present invention.

[0134] The PAK6 comprising the crystals of the invention may be isolated from any bacterial, plant, or animal source in which PAK6 is present. Within the scope of the present invention are proteins that are homologous to PAK6 that are derived from any biological kingdom. The PAK6 may be derived from a mammalian source, such as, for example, Homo sapiens. The crystals may comprise wild-type PAK6 or mutants of wild-type PAK6. Mutants of wild-type PAK6 are obtained by replacing at least one amino acid residue in the sequence of the wild-type PAK6 with a different amino acid residue, or by adding or deleting one or more amino acid residues within the wild-type sequence and/or at the N- and/or C-terminus of the wild-type PAK6. The mutants may, but not necessarily, crystallize under crystallization conditions that are substantially similar to those used to crystallize the wild-type PAK6.

[0135] The types of mutants contemplated by this invention include, but are not limited to, conservative mutants, non-conservative mutants, deletion mutants, truncated mutants, extended mutants, methionine mutants, selenomethionine mutants, cysteine mutants and selenocysteine mutants. A mutant may have, but need not display, PAK6 activity. A mutant may, for example, display biological activity that is substantially similar to that of the wild-type polypeptide. Methionine, selenomethione, cysteine, and selenocysteine mutants are particularly useful for producing heavy-atom derivative crystals, as described in detail, below.

[0136] It will be recognized by one of skill in the art that the types of mutants contemplated herein are not mutually exclusive; that is, for example, a polypeptide having a conservative mutation in one amino acid may in addition have a truncation of residues at the N-terminus, and several Ala, Leu, or Ile→Met mutations.

[0137] Sequence alignments of polypeptides in a protein family or of homologous polypeptide domains may be used to identify potential amino acid residues in the polypeptide sequence that are candidates for mutation. Identifying mutations that do not significantly interfere with the three-dimensional structure of PAK6 and/or that do not

deleteriously affect, and that may even enhance, the activity of PAK6 will depend, in part, on the region where the mutation occurs. In highly variable regions of the molecule, non-conservative substitutions as well as conservative substitutions may be tolerated without significantly disrupting the folding, the three-dimensional structure and/or the biological activity of the molecule. In highly conserved regions, or regions containing significant secondary structure, conservative amino acid substitutions may be tolerated.

[0138]   Conservative amino acid substitutions are well known in the art, and include substitutions made on the basis of a similarity in polarity, charge, solubility, hydrophobicity and/or the hydrophilicity of the amino acid residues involved. Typical conservative substitutions are those in which the amino acid is substituted with a different amino acid that is a member of the same class or category, as those classes are defined herein. Thus, typical conservative substitutions include aromatic to aromatic, apolar to apolar, aliphatic to aliphatic, acidic to acidic, basic to basic, polar to polar, etc. Other conservative amino acid substitutions are well known in the art. It will be recognized by those of skill in the art that generally, a total of 20% or fewer, typically 10% or fewer, most usually 5% or fewer, of the amino acids in the wild-type polypeptide sequence may be conservatively substituted with other amino acids without deleteriously affecting the biological activity, the folding, and/or the three-dimensional structure of the molecule, provided that such substitutions do not involve residues that are critical for activity, for example, critical binding pocket residues.

[0139]   In some embodiments, it may be desirable to make mutations in the active site of a protein, e.g., to reduce or completely eliminate protein activity. For example, it may be desirable to mutate important residues in the active site of a protease in order to reduce or eliminate protease activity and to avoid autolysis in solution or in a crystal. Thus, for example, in aspartyl proteases, the active site Asp residue may be mutated to an Ala or Asn residue to reduce protease activity. The active site Ser residue in serine proteases may be mutated to an Ala, Cys or Thr residue to reduce or eliminate protease activity. Similarly, the activity of a cysteine protease may be reduced or eliminated by mutating the active site Cys residue to an Ala, Ser or Thr residue. Other mutations that will reduce or completely eliminate the activity of a particular protein will be apparent to those of skill in the art.

[0140]   The amino acid residue Cys (C) is unusual in that it can form disulfide bridges with other Cys (C) residues or other sulfhydryls, such as, for example, sulfhydryl-

containing amino acids ("cysteine-like amino acids"). The ability of Cys (C) residues and other cysteine-like amino acids to exist in a polypeptide in either the reduced free -SH or oxidized disulfide-bridged form affects whether Cys (C) residues contribute net hydrophobic or hydrophilic character to a polypeptide. While Cys (C) exhibits a hydrophobicity of 0.29 according to the consensus scale of Eisenberg (Eisenberg *et al.*, J. Mol. Biol. 179:125-42, 1984), it is to be understood that for purposes of the present invention Cys (C) is categorized as a polar hydrophilic amino acid, notwithstanding the general classifications defined above. For example, Cys residues that are known to participate in disulfide bridges are not substituted or are conservatively substituted with other cysteine-like amino acids so that the residue can participate in a disulfide bridge. Typical cysteine-like residues include, for example, Pen, hCys, etc. Substitutions for Cys residues that interfere with crystallization are discussed *infra*.

[0141]   The structural coordinates of a binding pocket and/or of the protein may be used, for example, to engineer new molecules. These new molecules may be expressed in cells, for example, in plant cells using, for example, gene transformation, to improve nutrient yields in plant crops or to use plants to produce new molecules.

[0142]   While in most instances the amino acids of PAK6KD will be substituted with genetically-encoded amino acids, in certain circumstances mutants may include non-genetically encoded amino acids. For example, non-encoded derivatives of certain encoded amino acids, such as SeMet and/or SeCys, may be incorporated into the polypeptide chain using biological expression systems (such SeMet and SeCys mutants are described in more detail, *infra*).

[0143]   Alternatively, in instances where the mutant will be prepared in whole or in part by chemical synthesis, virtually any non-encoded amino acids may be used, ranging from D-isomers of the genetically encoded amino acids to non-encoded naturally-occurring natural and synthetic amino acids.

[0144]   Conservative amino acid substitutions for many of the commonly known non-genetically encoded amino acids are well known in the art. Conservative substitutions for other non-encoded amino acids may be determined based on their physical properties as compared to the properties of the genetically encoded amino acids.

[0145]   Those of ordinary skill in the art will recognize that substitutions, additions, and/or deletions that do not substantially alter the three dimensional structure of PAK6KD and that, for example, do not substantially alter the three dimensional structure of the

PAK6KD binding pocket or pockets discussed in the present application, are within the scope of the present invention. Such substitutions, additions, and/or deletions may be useful, for example, to provide convenient cloning sites in cDNA encoding PAK6, to aid in its purification, or to aid in obtaining crystallization.

[0146] These substitutions, deletions and/or additions include, but are not limited to, His tags, intein-containing self-cleaving tags, maltose binding protein fusions, glutathione S-transferase protein fusions, antibody fusions, green fluorescent protein fusions, signal peptide fusions, biotin accepting peptide fusions, tags that contain protease cleavage sites, and the like. Mutations may also be introduced into a polypeptide sequence where there are residues, *e.g.*, cysteine residues that interfere with crystallization. These cysteine residues may be substituted with an appropriate amino acid that does not readily form covalent bonds with other amino acid residues under crystallization conditions; *e.g.*, by substituting the cysteine with Ala, Ser or Gly. Any cysteine located in a non-helical or non-stranded segment, based on secondary structure assignments, are good candidates for replacement.

[0147] Mutants within the scope of the invention may or may not have PAK6 activity. Amino acid substitutions, additions and/or deletions that might alter or inhibit PAK6 activity are within the scope of the present invention. These mutants may be used in their crystalline form, or the molecular structure coordinates obtained therefrom, for example, to determine PAK6 structure and/or to provide phase information to aid the determination of the three-dimensional X-ray structures of other related or non-related crystalline polypeptides.

[0148] The heavy-atom derivative crystals from which the molecular structure coordinates of the invention are obtained generally comprise a crystalline PAK6KD polypeptide in association with one or more heavy atoms, such as, for example, Xe, Kr, Br, I, or a heavy metal atom. The polypeptide may correspond to a wild-type or a mutant PAK6KD, which may optionally be in co-complex with one or more molecules, as previously described. There are various types of heavy-atom derivatives of polypeptides: heavy-atom derivatives resulting from exposure of the protein to a heavy atom in solution, wherein crystals are grown in medium comprising the heavy atom, or in crystalline form, wherein the heavy atom diffuses into the crystal, heavy-atom derivatives wherein the polypeptide comprises heavy-atom containing amino acids, *e.g.*, selenomethionine and/or

selenocysteine, and heavy atom derivatives where the heavy atom is forced in under pressure, such as, for example, in a xenon chamber.

[0149] In practice, heavy-atom derivatives of the first type may be formed by soaking a native crystal in a solution comprising heavy metal atom salts, or organometallic compounds, *e.g.*, lead chloride, gold thiomalate, ethylmercurithiosalicylic acid-sodium salt (thimerosal), uranyl acetate, platinum tetrachloride, osmium tetraoxide, zinc sulfate, and cobalt hexamine, which can diffuse through the crystal and bind to the crystalline polypeptide.

[0150] Heavy-atom derivatives of this type can also be formed by adding to a crystallization solution comprising the polypeptide to be crystallized, an amount of a heavy metal atom salt, which may associate with the protein and be incorporated into the crystal. The location(s) of the bound heavy metal atom(s) may be determined by X-ray diffraction analysis of the crystal. This information, in turn, is used to generate the phase information needed to construct the three-dimensional structure of the protein.

[0151] Heavy-atom derivative crystals may also be prepared from polypeptides that include one or more SeMet and/or SeCys residues (SeMet and/or SeCys mutants). Such selenocysteine or selenomethionine mutants may be made from wild-type or mutant PAK6KD by expression of PAK6KD-encoding cDNAs in auxotrophic *E. coli* strains (Hendrickson *et al.*, EMBO J. 9(5):1665-72, 1990). In this method, the wild-type or mutant PAK6KD cDNA may be expressed in a host organism on a growth medium depleted of either natural cysteine or methionine (or both) but enriched in selenocysteine or selenomethionine (or both). Alternatively, selenocysteine or selenomethionine mutants may be made using nonauxotrophic *E. coli* strains, *e.g.*, by inhibiting methionine biosynthesis in these strains with high concentrations of Ile, Lys, Phe, Leu, Val or Thr and then providing selenomethionine in the medium (Doublié, Methods in Enzymology, 276:523-30, 1997). Furthermore, selenocysteine may be selectively incorporated into polypeptides by exploiting the prokaryotic and eukaryotic mechanisms for selenocysteine incorporation into certain classes of proteins *in vivo*, as described in U.S. Patent No. 5,700,660 to Leonard *et al.* (filed June 7, 1995). One of skill in the art will recognize that selenocysteine may, for example, not incorporated in place of cysteine residues that form disulfide bridges, as these may be important for maintaining the three-dimensional structure of the protein and may, for example, not be eliminated. One of skill in the art will further recognize that, in order to obtain accurate phase information, approximately

one selenium atom should be incorporated for every 140 amino acid residues of the polypeptide chain. The number of selenium atoms incorporated into the polypeptide chain may be conveniently controlled by designing a Met or Cys mutant having an appropriate number of Met and/or Cys residues, as described more fully below.

[0152]   In some instances, the polypeptide to be crystallized may not contain cysteine or methionine residues. Therefore, if selenomethionine and/or selenocysteine mutants are to be used to obtain heavy-atom derivative crystals, methionine and/or cysteine residues may be introduced into the polypeptide chain. Likewise, Cys residues must be introduced into the polypeptide chain if the use of a cysteine-binding heavy metal, such as mercury, is contemplated for production of a heavy-atom derivative crystal.

[0153]   Such mutations are, for example, introduced into the polypeptide sequence at sites that will not disturb the overall protein fold. For example, a residue that is conserved among many members of the protein family or that is thought to be involved in maintaining its activity or structural integrity, as determined by, e.g., sequence alignments, should not be mutated to a Met or Cys. In addition, conservative mutations, such as Ser to Cys, or Leu or Ile to Met, are, for example, introduced. One additional consideration is that, in order for a heavy-atom derivative crystal to provide phase information for structure determination, the location of the heavy atom(s) in the crystal unit cell must be determinable and provide phase information. Therefore, a mutation is, for example, not introduced into a portion of the protein that is likely to be mobile, e.g., at, or within 1-5 residues of, the N- and C-termini, or within loops.

[0154]   Conversely, if there are too many methionine and/or cysteine residues in a polypeptide sequence, over-incorporation of the selenium-containing side chains can lead to the inability of the polypeptide to fold and/or crystallize, and may potentially lead to complications in solving the crystal structure. In this case, methionine and/or cysteine mutants are prepared by substituting one or more of these Met and/or Cys residues with another residue. The considerations for these substitutions are the same as those discussed above for mutations that introduce methionine and/or cysteine residues into the polypeptide. Specifically, the Met and/or Cys residues are, for example, conservatively substituted with Leu/Ile and Ser, respectively.

[0155]   As DNA encoding cysteine and methionine mutants may be used in the methods described above for obtaining SeCys and SeMet heavy-atom derivative crystals, the Cys or Met mutant may have, for example, one Cys or Met residue for every 140 amino acids.

Production of Polypeptides

[0156] The native and mutated PAK6KD or PAK6 polypeptides described herein may be chemically synthesized in whole or part using techniques that are well known in the art (see, *e.g.*, Creighton, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., NY, 1983).

[0157] Gene expression systems may be used for the synthesis of native and mutated polypeptides. Expression vectors containing the native or mutated polypeptide coding sequence and appropriate transcriptional/translational control signals, that are known to those skilled in the art may be constructed. These methods include *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* recombination/genetic recombination. See, for example, the techniques described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY, 2001, and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY, 1989.

[0158] Host-expression vector systems may be used to express PAK6KD or PAK6. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing the coding sequence; yeast transformed with recombinant yeast expression vectors containing the coding sequence; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing the coding sequence; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing the coding sequence; or animal cell systems. The protein may also be expressed in human gene therapy systems, including, for example, expressing the protein to augment the amount of the protein in an individual, or to express an engineered therapeutic protein. The expression elements of these systems vary in their strength and specificities.

[0159] Specifically designed vectors allow the shuttling of DNA between hosts such as bacteria-yeast or bacteria-animal cells. An appropriately constructed expression vector may contain: an origin of replication for autonomous replication in host cells, one or more selectable markers, a limited number of useful restriction enzyme sites, a potential for high copy number, and active promoters. A promoter is defined as a DNA sequence that

directs RNA polymerase to bind to DNA and initiate RNA synthesis. A strong promoter is one that causes mRNAs to be initiated at high frequency.

[0160] The expression vector may also comprise various elements that affect transcription and translation, including, for example, constitutive and inducible promoters. These elements are often host and/or vector dependent. For example, when cloning in bacterial systems, inducible promoters such as the T7 promoter, pL of bacteriophage λ, plac, ptrp, ptac (ptrp-lac hybrid promoter) and the like may be used; when cloning in insect cell systems, promoters such as the baculovirus polyhedrin promoter may be used; when cloning in plant cell systems, promoters derived from the genome of plant cells (e.g., heat shock promoters; the promoter for the small subunit of RUBISCO; the promoter for the chlorophyll a/b binding protein) or from plant viruses (e.g., the 35S RNA promoter of CaMV; the coat protein promoter of TMV) may be used; when cloning in mammalian cell systems, mammalian promoters (e.g., metallothionein promoter) or mammalian viral promoters, (e.g., adenovirus late promoter; vaccinia virus 7.5K promoter; SV40 promoter; bovine papilloma virus promoter; and Epstein-Barr virus promoter) may be used.

[0161] Various methods may be used to introduce the vector into host cells, for example, transformation, transfection, infection, protoplast fusion, and electroporation. The expression vector-containing cells are clonally propagated and individually analyzed to determine whether they produce the appropriate polypeptides. Various selection methods, including, for example, antibiotic resistance, may be used to identify host cells that have been transformed. Identification of polypeptide expressing host cell clones may be done by several means, including but not limited to immunological reactivity with anti-PAK6KD or PAK6 antibodies, and the presence of host cell-associated activity.

[0162] Expression of cDNA may also be performed using *in vitro* produced synthetic mRNA. Synthetic mRNA may be efficiently translated in various cell-free systems, including but not limited to wheat germ extracts and reticulocyte extracts, as well as efficiently translated in cell-based systems, including, but not limited, to microinjection into frog oocytes.

[0163] To determine the cDNA sequence(s) that yields optimal levels of activity and/or protein, modified cDNA molecules are constructed. A non-limiting example of a modified cDNA is where the codon usage in the cDNA has been optimized for the host cell in which the cDNA will be expressed. Host cells are transformed with the cDNA molecules and the levels of PAK6KD or PAK6 RNA and/or protein are measured.

[0164] Levels of PAK6 or PAK6KD protein in host cells are quantitated by a variety of methods such as immunoaffinity and/or ligand affinity techniques, PAK6 or PAK6KD-specific affinity beads or specific antibodies are used to isolate ^{35}S-methionine labeled or unlabeled protein. Labeled or unlabeled protein is analyzed by SDS-PAGE. Unlabeled protein is detected by Western blotting, ELISA or RIA employing specific antibodies.

[0165] Following expression of PAK6 or PAK6KD in a recombinant host cell, polypeptides may be recovered to provide the protein in active form. Several purification procedures are available and suitable for use. Recombinant PAK6 or PAK6KD may be purified from cell lysates or from conditioned culture media, by various combinations of, or individual application of, fractionation, or chromatography steps that are known in the art.

[0166] In addition, recombinant PAK6 or PAK6KD may be separated from other cellular proteins by use of an immuno-affinity column made with monoclonal or polyclonal antibodies specific for full length nascent protein or polypeptide fragments thereof. Other affinity based purification techniques known in the art may also be used.

[0167] Alternatively, the polypeptides may be recovered from a host cell in an unfolded, inactive form, e.g., from inclusion bodies of bacteria. Proteins recovered in this form may be solubilized using a denaturant, e.g., guanidinium hydrochloride, and then refolded into an active form using methods known to those skilled in the art, such as dialysis.

Crystallization Of Polypeptides And Characterization Of Crystal

[0168] Various methods known in the art may be used to produce the native and heavy-atom derivative crystals of the present invention. Methods include, but are not limited to, batch, liquid bridge, dialysis, and vapor diffusion (see, e.g., McPherson, Crystallization of Biological Macromolecules, Cold Spring Harbor Press, New York, 1998; McPherson, Eur. J. Biochem. 189:1-23, 1990; Weber, Adv. Protein Chem. 41:1-36, 1991; Methods in Enzymology 276:13-22, 100-110; 131-143, Academic Press, San Diego, 1997).

[0169] Generally, native crystals are grown by dissolving substantially pure polypeptide in an aqueous buffer containing a precipitant at a concentration just below that necessary to precipitate the protein. Examples of precipitants include, but are not limited to, polyethylene glycol, ammonium sulfate, 2-methyl-2,4-pentanediol, sodium citrate, sodium chloride, glycerol, isopropanol, lithium sulfate, sodium acetate, sodium formate,

potassium sodium tartrate, ethanol, hexanediol, ethylene glycol, dioxane, t-butanol and combinations thereof. Water is removed by controlled evaporation to produce precipitating conditions, which are maintained until crystal growth ceases.

[0170]   In one embodiment, native crystals are grown by vapor diffusion in hanging drops or sitting drops (McPherson, Preparation and Analysis of Protein Crystals, John Wiley, New York, 1982; McPherson, Eur. J. Biochem. 189:1-23, 1990). Generally, up to about 25 μL, or up to about 5μl, 3μl, or 2μl, of substantially pure polypeptide solution is mixed with a volume of reservoir solution. The ratio may vary according to biophysical conditions, for example, the ratio of protein volume: reservoir volume in the drop may be 1:1, giving a precipitant concentration about half that required for crystallization. Those of ordinary skill in the art recognize that the drop and reservoir volumes may be varied within certain biophysical conditions and still allow crystallization. In the sitting drop method, the polypeptide/precipitant solution is allowed to equilibrate in a closed container with a larger aqueous reservoir having a precipitant concentration optimal for producing crystals. In the hanging drop method, the polypeptide solution mixed with reservoir solution is suspended as a droplet underneath, for example, a coverslip, which is sealed onto the top of the reservoir. For both methods, the sealed container is allowed to stand, usually, for example, for up to 2-6 weeks, until crystals grow. The drop may be checked periodically to determine if a crystal has formed. One way of viewing the drop is using, for example, a microscope. One method of checking the drop, for high throughput purposes, includes methods that may be found in, for example, U.S. Utility Patent Application 10/042,929, filed October 18, 2001, entitled "Apparatus and Method for Identification of Crystals By In-situ X-Ray Diffraction." Such methods include, for example, using an automated apparatus comprising a crystal growing incubator, an X-ray source adjacent to the crystal growing incubator, where the X-ray source is configured to irradiate the crystalline material grown in the crystal growing incubator, and an X-ray detector configured to detect the presence of the diffracted X-rays from crystalline material grown in the incubator. In some examples, a charge coupled video camera is included in the detector system.

[0171]   Those having skill in the art will recognize that the above-described crystallization conditions may be varied. Such variations may be used alone or in combination, and may include various volumes of protein solution and reservoir solution known to those of ordinary skill in the art. Other buffer solutions may be used such as

Tris, imidazole, or MOPS buffer, so long as the desired pH range is maintained, and the chemical composition of the buffer is compatible with crystal formation. Compounds or other ligands may be added to the crystallization solution in order to obtain co-crystals.

[0172]   Heavy-atom derivative crystals may be obtained by soaking native crystals in mother liquor containing salts of heavy metal atoms and can also be obtained from SeMet and/or SeCys mutants, as described above for native crystals.

[0173]   Mutant proteins may crystallize under slightly different crystallization conditions than wild-type protein, or under very different crystallization conditions, depending on the nature of the mutation, and its location in the protein. For example, a non-conservative mutation may result in alteration of the hydrophilicity of the mutant, which may in turn make the mutant protein either more soluble or less soluble than the wild-type protein. Typically, if a protein becomes more hydrophilic as a result of a mutation, it will be more soluble than the wild-type protein in an aqueous solution and a higher precipitant concentration will be needed to cause it to crystallize. Conversely, if a protein becomes less hydrophilic as a result of a mutation, it will be less soluble in an aqueous solution and a lower precipitant concentration will be needed to cause it to crystallize. If the mutation happens to be in a region of the protein involved in crystal lattice contacts, crystallization conditions may be affected in more unpredictable ways.

Characterization of Crystals

[0174]   The dimensions of a unit cell of a crystal are defined by six numbers, the lengths of three unique edges, a, b, and c, and three unique angles α, β, and γ. The type of unit cell that comprises a crystal is dependent on the values of these variables, as discussed above.

[0175]   When a crystal is exposed to an X-ray beam, the electrons of the molecules in the crystal diffract the beam such that there is a sphere of diffracted X-rays around the crystal. The angle at which diffracted beams emerge from the crystal may be computed by treating diffraction as if it were reflection from sets of equivalent, parallel planes of atoms in a crystal (Bragg's Law). The most obvious sets of planes in a crystal lattice are those that are parallel to the faces of the unit cell. These and other sets of planes may be drawn through the lattice points. Each set of planes is identified by three indices, hkl. The h index gives the number of parts into which the a edge of the unit cell is cut, the k index gives the number of parts into which the b edge of the unit cell is cut, and the l index gives

the number of parts into which the c edge of the unit cell is cut by the set of hkl planes. Thus, for example, the 235 planes cut the a edge of each unit cell into halves, the b edge of each unit cell into thirds, and the c edge of each unit cell into fifths. Planes that are parallel to the bc face of the unit cell are the 100 planes; planes that are parallel to the ac face of the unit cell are the 010 planes; and planes that are parallel to the ab face of the unit cell are the 001 planes.

[0176] When a detector is placed in the path of the diffracted X-rays, in effect cutting into the sphere of diffraction, a series of spots, or reflections, may be recorded of a still crystal (not rotated) to produce a "still" diffraction pattern. Each reflection is the result of X-rays reflecting off one set of parallel planes, and is characterized by an intensity, which is related to the distribution of molecules in the unit cell, and hkl indices, which correspond to the parallel planes from which the beam producing that spot was reflected. If the crystal is rotated about an axis perpendicular to the X-ray beam, a large number of reflections are recorded on the detector, resulting in a diffraction pattern.

[0177] The unit cell dimensions and space group of a crystal may be determined from its diffraction pattern. First, the spacing of reflections is inversely proportional to the lengths of the edges of the unit cell. Therefore, if a diffraction pattern is recorded when the X-ray beam is perpendicular to a face of the unit cell, two of the unit cell dimensions may be deduced from the spacing of the reflections in the x and y directions of the detector, the crystal-to-detector distance, and the wavelength of the X-rays. Those of skill in the art will appreciate that, in order to obtain all three unit cell dimensions, the crystal must be rotated such that the X-ray beam is perpendicular to another face of the unit cell. Second, the angles of a unit cell may be determined by the angles between lines of spots on the diffraction pattern. Third, the absence of certain reflections and the repetitive nature of the diffraction pattern, which may be evident by visual inspection, indicate the internal symmetry, or space group, of the crystal. Therefore, a crystal may be characterized by its unit cell and space group, as well as by its diffraction pattern.

[0178] Once the dimensions of the unit cell are determined, the likely number of polypeptides in the asymmetric unit may be deduced from the size of the polypeptide, the density of the average protein, and the typical solvent content of a protein crystal, which is usually in the range of 30-70% of the unit cell volume (Matthews, J. Mol. Biol. 33(2):491-97, 1968).

Collection of Data and Determination of Structure Solutions

[0179]   The diffraction pattern is related to the three-dimensional shape of the molecule by a Fourier transform. The process of determining the solution is in essence a re-focusing of the diffracted X-rays to produce a three-dimensional image of the molecule in the crystal. Since re-focusing of X-rays cannot be done with a lens at this time, it is done via mathematical operations.

[0180]   The sphere of diffraction has symmetry that depends on the internal symmetry of the crystal, which means that certain orientations of the crystal will produce the same set of reflections. Thus, a crystal with high symmetry has a more repetitive diffraction pattern, and there are fewer unique reflections that need to be recorded in order to have a complete representation of the diffraction. The goal of data collection, a dataset, is a set of consistently measured, indexed intensities for as many reflections as possible. A complete dataset is collected if at least 80%, preferably at least 90%, most preferably at least 95% of unique reflections are recorded. In one embodiment, a complete dataset is collected using one crystal. In another embodiment, a complete dataset is collected using more than one crystal of the same type.

[0181]   Sources of X-rays include, but are not limited to, a rotating anode X-ray generator such as a Rigaku RU-200, a micro source or mini-source, a sealed-beam source, or a beam line at a synchrotron light source, such as the Advanced Photon Source at Argonne National Laboratory. Suitable detectors for recording diffraction patterns include, but are not limited to, X-ray sensitive film, multiwire area detectors, image plates coated with phosphorus, and CCD cameras. Typically, the detector and the X-ray beam remain stationary, so that, in order to record diffraction from different parts of the crystal's sphere of diffraction, the crystal itself is moved via an automated system of moveable circles called a goniostat.

[0182]   One of the biggest problems in data collection, particularly from macromolecular crystals having a high solvent content, is the rapid degradation of the crystal in the X-ray beam. In order to slow the degradation, data is often collected from a crystal at liquid nitrogen temperatures. In order for a crystal to survive the initial exposure to liquid nitrogen, the formation of ice within the crystal may be prevented by the use of a cryoprotectant. Suitable cryoprotectants include, but are not limited to, low molecular weight polyethylene glycols, ethylene glycol, sucrose, glycerol, xylitol, and combinations thereof. Crystals may be soaked in a solution comprising the one or more cryoprotectants

prior to exposure to liquid nitrogen, or the one or more cryoprotectants may be added to the crystallization solution. Data collection at liquid nitrogen temperatures may allow the collection of an entire dataset from one crystal.

[0183]   Once a dataset is collected, the information is used to determine the three-dimensional structure of the molecule in the crystal. This phase information may be acquired by methods described below in order to perform a Fourier transform on the diffraction pattern to obtain the three-dimensional structure of the molecule in the crystal. It is the determination of phase information that in effect refocuses X-rays to produce the image of the molecule.

[0184]   One method of obtaining phase information is by isomorphous replacement, in which heavy-atom derivative crystals are used. In this method, the positions of heavy atoms bound to the molecules in the heavy-atom derivative crystal are determined, and this information is then used to obtain the phase information necessary to elucidate the three-dimensional structure of a native crystal (Blundell *et al.*, Protein Crystallography, Academic Press, 1976).

[0185]   Another method of obtaining phase information is by molecular replacement, which is a method of calculating initial phases for a new crystal of a polypeptide whose structure coordinates are unknown by orienting and positioning a polypeptide whose structure coordinates are known within the unit cell of the new crystal so as to best account for the observed diffraction pattern of the new crystal. Phases are then calculated from the oriented and positioned polypeptide and combined with observed amplitudes to provide an approximate Fourier synthesis of the structure of the molecules comprising the new crystal (Lattman, Methods in Enzymology 115:55-77, 1985; Rossmann, "The Molecular Replacement Method," Int. Sci. Rev. Ser. No. 13, Gordon & Breach, New York, 1972).

[0186]   A third method of phase determination is multi-wavelength anomalous diffraction or MAD. In this method, X-ray diffraction data are collected at several different wavelengths from a single crystal containing at least one heavy atom with absorption edges near the energy of incoming X-ray radiation. The resonance between X-rays and electron orbitals leads to differences in X-ray scattering that permits the locations of the heavy atoms to be identified, which in turn provides phase information for a crystal of a polypeptide. A detailed discussion of MAD analysis may be found in Hendrickson,

Trans. Am. Crystallogr. Assoc., 21:11, 1985; Hendrickson *et al.*, EMBO J. 9:1665, 1990; and Hendrickson, Science, 254:51-58, 1991).

[0187] A fourth method of determining phase information is single wavelength anomalous dispersion or SAD. In this technique, X-ray diffraction data are collected at a single wavelength from a single native or heavy-atom derivative crystal, and phase information is extracted using anomalous scattering information from atoms such as sulfur or chlorine in the native crystal or from the heavy atoms in the heavy-atom derivative crystal. The wavelength of X-rays used to collect data for this phasing technique need not be close to the absorption edge of the anomalous scatterer. A detailed discussion of SAD analysis may be found in Brodersen, et al., Acta Cryst., D56:431-41, 2000.

[0188] A fifth method of determining phase information is single isomorphous replacement with anomalous scattering or SIRAS. SIRAS combines isomorphous replacement and anomalous scattering techniques to provide phase information for a crystal of a polypeptide. X-ray diffraction data are collected at a single wavelength, usually from both a native and a single heavy-atom derivative crystal. Phase information obtained only from the location of the heavy atoms in a single heavy-atom derivative crystal leads to an ambiguity in the phase angle, which is resolved using anomalous scattering from the heavy atoms. Phase information is extracted from both the location of the heavy atoms and from anomalous scattering of the heavy atoms. A detailed discussion of SIRAS analysis may be found in North, Acta Cryst. 18:212-16, 1965; Matthews, Acta Cryst. 20:82-86, 1966; Methods in Enzymology 276:530-37, 1997.

[0189] Once phase information is obtained, it is combined with the diffraction data to produce an electron density map, an image of the electron clouds surrounding the atoms that constitute the molecules in the unit cell. The higher the resolution of the data, the more distinguishable the features of the electron density map, because atoms that are closer together are resolvable. A model of the macromolecule is then built into the electron density map with the aid of a computer, using as a guide all available information, such as the polypeptide sequence and the established rules of molecular structure and stereochemistry. Interpreting the electron density map is a process of finding the chemically reasonable conformation that fits the map precisely.

[0190] After a model is generated, a structure is refined. Refinement is the process of minimizing the function ϕ, which is the difference between observed and calculated intensity values (measured by an R-factor), and which is a function of the position,

temperature factor, and occupancy of each non-hydrogen atom in the model. This usually involves alternate cycles of real space refinement, *i.e.*, calculation of electron density maps and model building, and reciprocal space refinement, *i.e.*, computational attempts to improve the agreement between the original intensity data and intensity data generated from each successive model. Refinement ends when the function ϕ converges on a minimum wherein the model fits the electron density map and is stereochemically and conformationally reasonable. During the last stages of refinement, ordered solvent molecules are added to the structure.

Structures of PAK6KD

[0191] The present invention provides, for the first time, the high-resolution three-dimensional structures and molecular structure coordinates of crystalline PAK6KD as determined by X-ray crystallography.

[0192] Contemplated within the scope of the present invention are any set of structure coordinates obtained for crystals of PAK6KD, whether native crystals, heavy-atom derivative crystals or co-crystals, that have a root mean square deviation ("r.m.s.d.") of up to about or equal to 1.5Å, preferably 1.25Å, preferably 1Å, preferably 1.75Å, and preferably 0.5Å when superimposed, using backbone atoms (N, C-α, C and O), or using C-α atoms, on the structure coordinates listed in Fig. 4 are considered to be within the scope of the present invention when at least 50% to 100% of the backbone atoms of PAK6KD are included in the superposition. The amino acid numbers in Figure 4 reflect the amino acid position in the expressed protein used to obtain the crystals of the present invention. Those of ordinary skill in the art may align the sequence with other sequences of PAK6KD or PAK6 to, if desired, correlate the amino acid residue number with the Figure 4 sequence or the wild type sequence numbers.

Structure Coordinates

[0193] The molecular structure coordinates may be used in molecular modeling and design, as described more fully below. The present invention encompasses the structure coordinates and other information, *e.g.*, amino acid sequence, connectivity tables, vector-based representations, temperature factors, etc., used to generate the three-dimensional

structure of the polypeptide for use in the software programs described below and other software programs.

[0194] The invention includes methods of producing computer readable databases comprising the three-dimensional molecular structure coordinates of certain molecules, including, for example, the PAK6KD structure coordinates, the structure coordinates of binding pockets or active sites of PAK6KD, or structure coordinates of compounds capable of binding to PAK6KD. The databases of the present invention may comprise any number of sets of molecular structure coordinates for any number of molecules, including, for examples, structure coordinates of one molecule. In other embodiments, the databases of the present invention may comprise structure coordinates of a compound or compounds that have been identified by virtual screening to bind to a PAK6 binding pocket, or other representations of such compounds such as, for example, a graphic representation or a name. By "database" is meant a collection of retrievable data. The invention encompasses machine readable media embedded with or containing information regarding the three-dimensional structure of a crystalline polypeptide and/or model, such as, for example, its molecular structure coordinates, described herein, or with subunits, domains, and/or, portions thereof such as, for example, portions comprising active sites, accessory binding sites, and/or binding pockets in either liganded or unliganded forms. Alternatively, the information may be that of identifiers which represent specific structures found in a protein. As used herein, "machine readable medium" refers to any medium that may be read and accessed directly by a computer or scanner. Such media may take many forms, including but not limited to, non-volatile, volatile and transmission media. Non-volatile media, i.e., media that can retain information in the absence of power, includes a ROM. Volatile media, i.e., media that cannot retain information in the absence of power, includes a main memory. Transmission media includes coaxial cables, copper wire and fiber optics, including the wires that comprise the bus. Transmission media can also take the form of carrier waves; i.e., electromagnetic waves that may be modulated, as in frequency, amplitude or phase, to transmit information signals. Additionally, transmission media can take the form of acoustic or light waves, such as those generated during radio wave and infrared data communications.

[0195] Such media also include, but are not limited to: magnetic storage media, such as floppy discs, flexible discs, hard disc storage medium and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM or

ROM, PROM (i.e., programmable read only memory), EPROM (i.e., erasable programmable read only memory), including FLASH-EPROM, any other memory chip or cartridge, carrier waves, or any other medium from which a processor can retrieve information, and hybrids of these categories such as magnetic/optical storage media. Such media further include paper on which is recorded a representation of the molecular structure coordinates, *e.g.*, Cartesian coordinates, that may be read by a scanning device and converted into a format readily accessed by a computer or by any of the software programs described herein by, for example, optical character recognition (OCR) software. Such media also include physical media with patterns of holes, such as, for example, punch cards, and paper tape.

[0196] A variety of data storage structures are available for creating a computer readable medium having recorded thereon the molecular structure coordinates of the invention or portions thereof and/or X-ray diffraction data. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats may be used to store the sequence and X-ray data information on a computer readable medium. Such formats include, but are not limited to, macromolecular Crystallographic Information File ("mmCIF") and Protein Data Bank ("PDB") format (Research Collaboratory for Structural Bioinformatics; www.rcsb.org; Cambridge Crystallographic Data Centre format (www.ccdc.can.ac.uk/support/csd_doc/volume3/z323.html); Structure-data ("SD") file format (MDL Information Systems, Inc.; Dalby, *et al.*, J. Chem. Inf. Comp. Sci., 32:244-55, 1992; and line-notation, *e.g.*, as used in SMILES (Weininger, J. Chem. Inf. Comp. Sci. 28:31-36, 1988). Methods of converting between various formats read by different computer software will be readily apparent to those of skill in the art, *e.g.*, BABEL (v. 1.06, Walters & Stahl, ©1992, 1993, 1994; www.brunel.ac.uk/departments/chem/babel.htm). All format representations of the polypeptide coordinates described herein, or portions thereof, are contemplated by the present invention. By providing computer readable medium having stored thereon the atomic coordinates of the invention, one of skill in the art can routinely access the atomic coordinates of the invention, or portions thereof, and related information for use in modeling and design programs, described in detail below.

[0197] A computer may be used to display the structure coordinates or the three-dimensional representation of the protein or peptide structures, or portions thereof, such

as, for example, portions comprising active sites, accessory binding sites, and/or binding pockets, in either liganded or unliganded form, of the present invention. The term "computer" includes, but is not limited to, mainframe computers, personal computers, portable laptop computers, and personal data assistants ("PDAs") which can store data and independently run one or more applications, i.e., programs. The computer may include, for example, a machine readable storage medium of the present invention, a working memory for storing instructions for processing the machine-readable data encoded in the machine readable storage medium, a central processing unit operably coupled to the working memory and to the machine readable storage medium for processing the machine readable information, and a display operably coupled to the central processing unit for displaying the structure coordinates or the three-dimensional representation. The information contained in the machine-readable medium may be in the form of, for example, X-ray diffraction data, structure coordinates, electron density maps, or ribbon structures. The information may also include such data for co-complexes between a compound and a protein or peptide of the present invention.

[0198]   The computers of the present invention may also include, for example, a central processing unit, a working memory which may be, for example, random-access memory (RAM) or "core memory," mass storage memory (for example, one or more disk drives or CD-ROM drives), one or more cathode-ray tube ("CRT") display terminals or one or more LCD displays, one or more keyboards, one or more input lines, and one or more output lines, all of which are interconnected by a conventional bi-directional system bus. Machine-readable data of the present invention may be inputted and/or outputted through a modem or modems connected by a telephone line or a dedicated data line (either of which may include, for example, wireless modes of communication). The input hardware may also (or instead) comprise CD-ROM drives or disk drives. Other examples of input devices are a keyboard, a mouse, a trackball, a finger pad, or cursor direction keys. Output hardware may also be implemented by conventional devices. For example, output hardware may include a CRT, or any other display terminal, a printer, or a disk drive. The CPU coordinates the use of the various input and output devices, coordinates data accesses from mass storage and accesses to and from working memory, and determines the order of data processing steps. The computer may use various software programs to process the data of the present invention. Examples of many of these types of software are discussed throughout the present application.

[0199] Those of skill in the art will recognize that a set of structure coordinates is a relative set of points that define a shape in three dimensions. Therefore, two different sets of coordinates could define the identical or a similar shape. Also, minor changes in the individual coordinates may have very little effect on the peptide's shape. Minor changes in the overall structure may have very little to no effect, for example, on the binding pocket, and would not be expected to significantly alter the nature of compounds that might associate with the binding pocket.

[0200] Although Cartesian coordinates are important and convenient representations of the three-dimensional structure of a polypeptide, other representations of the structure are also useful. Therefore, the three-dimensional structure of a polypeptide, as discussed herein, includes not only the Cartesian coordinate representation, but also all alternative representations of the three-dimensional distribution of atoms. For example, atomic coordinates may be represented as a Z-matrix, wherein a first atom of the protein is chosen, a second atom is placed at a defined distance from the first atom, and a third atom is placed at a defined distance from the second atom so that it makes a defined angle with the first atom. Each subsequent atom is placed at a defined distance from a previously placed atom with a specified angle with respect to the third atom, and at a specified torsion angle with respect to a fourth atom. Atomic coordinates may also be represented as a Patterson function, wherein all interatomic vectors are drawn and are then placed with their tails at the origin. This representation is particularly useful for locating heavy atoms in a unit cell. In addition, atomic coordinates may be represented as a series of vectors having magnitude and direction and drawn from a chosen origin to each atom in the polypeptide structure. Furthermore, the positions of atoms in a three-dimensional structure may be represented as fractions of the unit cell (fractional coordinates), or in spherical polar coordinates.

[0201] Additional information, such as thermal parameters, which measure the motion of each atom in the structure, chain identifiers, which identify the particular chain of a multi-chain protein in which an atom is located, and connectivity information, which indicates to which atoms a particular atom is bonded, is also useful for representing a three-dimensional molecular structure.

[0202] The structural information of a compound that binds a PAK6KD of the invention may be similarly stored and transmitted as described above for structural information of PAK6KD.

Uses of the Molecular Structure Coordinates

[0203]   Structure information, typically in the form of molecular structure coordinates, may be used in a variety of computational or computer-based methods to, for example, design, screen for, and/or identify compounds that bind the crystallized polypeptide or a portion or fragment thereof, or to intelligently design mutants that have altered biological properties.

[0204]   When designing or identifying compounds that may associate with a given protein, binding pockets are often analyzed. The term "binding pocket," refers to a region of a protein that, because of its shape, likely associates with a chemical entity or compound. A binding pocket may be the same as an active site. A binding pocket of a protein is usually involved in associating with the protein's natural ligands or substrates, and is often the basis for the protein's activity. A binding pocket may refer to an active site. Many drugs act by associating with a binding pocket of a protein. A binding pocket may comprise amino acid residues that line the cleft of the pocket. Those of ordinary skill in the art will recognize that the numbering system used for other isoforms of PAK6KD may be different, but that the corresponding amino acids may be determined with a homology software program known to those of ordinary skill in the art. A binding pocket homolog comprises amino acids having structure coordinates that have a root mean square deviation from structure coordinates, as indicated in Fig. 4, of the binding pocket amino acids of up to about 1.5Å, preferably up to about 1.25Å, preferably up to about 1Å, preferably up to about 0.75Å, preferably up to about 0.5Å, and preferably up to about 0.25Å.

[0205]   Where a binding pocket or regulatory site is said to comprise amino acids having particular structure coordinates, the amino acids comprise the same amino acid residues, or may comprise amino acids having similar properties, as shown in, for example, Table 1, and have either the same relative three-dimensional structure coordinates as Fig. 4, or the group of amino acid residues named as part of the binding pocket have an rmsd of within 1.5Å, preferably within 1.25Å, preferably within 1Å, preferably within 0.75Å, preferably within 0.5Å, and preferably within 0.25Å of the structure coordinates of Fig. 4. Preferably, when comparing the structure coordinates of the backbone atoms of the amino acid residues, the rmsd is within 1.5Å, preferably within

1.25Å, preferably within 1Å, preferably within 0.75Å, preferably within 0.5Å, and more preferably within 0.25Å.

[0206] Software applications are available to compare structures, or portions thereof, to determine if they are sufficiently similar to the structures of the invention such as DALI (Holm and Sander, *J. Mol. Biol.* 233:123-38, 1993; (See European Bioinformatics Institute site at www.ebi.ac.uk/); MOE (Chemical Computing Group, Inc. Montreal, Quebec, Canada; and DEJAVU (Uppsala Software Factory; Kleywegt, G.S. & Jones, T.A., "Detecting Folding Motifs and Similarities in Protein Structure," *Methods in Enzymology*, 277:525-45, 1997).

[0207] The crystals and structure coordinates obtained therefrom may be used for rational drug design to identify and/or design compounds that bind PAK6 as an approach towards developing new therapeutic agents. For example, a high resolution X-ray structure of, for example, a crystallized protein saturated with solvent, will often show the locations of ordered solvent molecules around the protein, and in particular at or near putative binding pockets of the protein. This information can then be used to design molecules that bind these sites, the compounds synthesized and tested for binding in biological assays (Travis, *Science*, 262:1374, 1993).

[0208] The structure may also be computationally screened with a plurality of molecules to determine their ability to bind to the PAK6KD at various sites. Such compounds may be used as targets or leads in medicinal chemistry efforts to identify, for example, inhibitors of potential therapeutic importance (Travis, *Science*, 262:1374, 1993). The three dimensional structures of such compounds may be superimposed on a three dimensional representation of PAK6KD or an active site or binding pocket thereof to assess whether the compound fits spatially into the representation and hence the protein. Structural information produced by such methods and concerning a compound that fits (or a fitting portion of such a compound) may be stored in a machine readable medium. Alternatively, one or more identifiers of a compound that fits, or a fitting portion thereof, may be stored in a machine readable medium. Examples of identifiers include chemical name or abbreviation, chemical or molecular formula, chemical structure, and/or other identifying information. As an non-limiting example, if the three dimensional structure of phenol is found to fit the active site of PAK6KD, the structural information of phenol, or the portion that fits, may be stored for further use. Alternatively, an identifier of phenol, or of the portion that fits, such as the -OH group, may be stored for further use. Other

identifying information for phenol may also be used to represent it. All storage of information concerning a compound that fits may optionally be in combination with one or more pieces of information concerning PAK6KD.

[0209] In an analogous manner, the structure of PAK6KD or an active site or binding pocket thereof may be used to computationally screen small molecule databases for chemical entities or compounds that can bind in whole, or in part, to PAK6. In this screening, the quality of fit of such entities or compounds to the binding pocket may be judged either by shape complementarity or by estimated interaction energy (Meng, *et al.*, *J. Comp. Chem.* 13:505-24, 1992).

[0210] In still another embodiment, compounds may be developed that are analogues of natural substrates, reaction intermediates or reaction products of PAK6. The reaction intermediates of PAK6 may be deduced from the substrates, or reaction products in co-complex with PAK6KD. The binding of substrates, reaction intermediates, and reaction products may change the conformation of the binding pocket, which provides additional information regarding binding patterns of potential ligands, activators, inhibitors, and the like. Such information is also useful to design improved analogues of known PAK6 inhibitors or to design novel classes of inhibitors based on the substrates, reaction intermediates, and reaction products of PAK6KD and PAK6KD-inhibitor co-complexes. This provides a novel route for designing PAK6KD inhibitors with both high specificity and stability.

[0211] Another method of screening or designing compounds that associate with a binding pocket includes, for example, computationally designing a negative image of the binding pocket. This negative image may be used to identify a set of pharmacophores. A pharmacophore may be a description of functional groups and how they relate to each other in three-dimensional space. This set of pharmacophores may be used to design compounds and screen chemical databases for compounds that match with the pharmacophore(s). Compounds identified by this method may then be further evaluated computationally or experimentally for binding activity. Various computer programs may be used to create the negative image of the binding pocket, for example; GRID (Goodford, J. Med. Chem. 28:849-57, 1985; GRID is available from Oxford University, Oxford, UK); MCSS (Miranker & Karplus, Proteins: Structure, Function and Genetics 11:29-34, 1991; MCSS is available from Accelrys, Inc., San Diego, CA); LUDI (Bohm, J. Comp. Aid. Molec. Design 6:61-78, 1992; LUDI is available from Accelrys, Inc., San Diego, CA);

DOCK (Kuntz et al.; *J. Mol. Biol.* 161:269-88, 1982; DOCK is available from University of California, San Francisco, CA); DOCKIT (Metaphorics, Mission Viejo, CA) and MOE. Other appropriate programs are desribed in, for example, Halperin, et al., Proteins 47(4): 409-43 (2002).

[0212] Thus, among the various embodiments of the present invention are methods of identifying, screening, and designing compounds that associate with a binding pocket of PAK6KD.

[0213] The design of compounds that bind to and/or modulate PAK6, for example that inhibit or activate PAK6 according to this invention generally involves consideration of two factors. First, the compound must be capable of physically and structurally associating, either covalently or non-covalently with PAK6. For example, covalent interactions may be important for designing irreversible or suicide inhibitors of a protein. Non-covalent molecular interactions important in the association of PAK6 with the compound include hydrogen bonding, ionic interactions and van der Waals and hydrophobic interactions. Second, the compound must be able to assume a conformation and orientation in relation to the binding pocket, that allows it to associate with PAK6. Although certain portions of the compound will not directly participate in this association with PAK6, those portions may still influence the overall conformation of the molecule and may have a significant impact on potency. Conformational requirements include the overall three-dimensional structure and orientation of the chemical group or compound in relation to all or a portion of the binding pocket, or the spacing between functional groups of a compound comprising several chemical groups that directly interact with PAK6.

[0214] Computer modeling techniques may be used to assess the potential modulating or binding effect of a chemical compound on PAK6KD. If computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to PAK6 and affect (by inhibiting or activating) its activity.

[0215] Modulating or other binding compounds of PAK6 may be computationally evaluated and designed by means of a series of steps in which chemical groups or fragments are screened and selected for their ability to associate with the individual binding pockets or other areas of PAK6. Several methods are available to screen chemical groups or fragments for their ability to associate with PAK6. This process may begin by visual inspection of, for example, the active site on the computer screen based on the PAK6KD coordinates. Selected fragments or chemical groups may then be positioned in

a variety of orientations, or docked, within an individual binding pocket of PAK6KD (Blaney, J.M. and Dixon, J.S., *Perspectives in Drug Discovery and Design*, 1:301, 1993). Manual docking may be accomplished using software such as Insight II (Accelrys, San Diego, CA) MOE; CE (Shindyalov, IN, Bourne, PE, "Protein Structure Alignment by Incremental Combinatorial Extension (CE) of the Optimal Path," *Protein Engineering*, 11:739-47, 1998); and SYBYL (Molecular Modeling Software, Tripos Associates, Inc., St. Louis, MO, 1992), followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM (Brooks, *et al.*, *J. Comp. Chem.* 4:187-217, 1983). More automated docking may be accomplished by using programs such as DOCK (Kuntz *et al.*, *J. Mol. Biol.*, 161:269-88, 1982; DOCK is available from University of California, San Francisco, CA); AUTODOCK (Goodsell & Olsen, Proteins: Structure, Function, and Genetics 8:195-202, 1990; AUTODOCK is available from Scripps Research Institute, La Jolla, CA); GOLD (Cambridge Crystallographic Data Centre (CCDC); Jones et al., *J. Mol. Biol.* 245:43-53, 1995); and FLEXX (Tripos, St. Louis, MO; Rarey, M., et al., *J. Mol. Biol.* 261:470-89, 1996); AMBER (Weiner, *et al.*, *J. Am. Chem. Soc.* 106:765-84, 1984) and C^2 MMFF (Merck Molecular Force Field; Accelrys, San Diego, CA). Other appropriate programs are described in, for example, Halperin, et al.

[0216]   Specialized computer programs may also assist in the process of selecting fragments or chemical groups. These include DOCK; GOLD; LUDI; FLEXX (Tripos, St. Louis, MO; Rarey, M., et al., *J. Mol. Biol.* 261:470-89, 1996); and GLIDE (Eldridge, et al., *J. Comput. Aided Mol. Des.* 11:425-45, 1997; Schrödinger, Inc., New York). Other appropriate programs are described in, for example, Halperin, et al., (Portland, OR).

[0217]   Once suitable chemical groups or fragments have been selected, they may be assembled into a single compound or inhibitor. Assembly may proceed by visual inspection of the relationship of the fragments to each other in the three-dimensional image displayed on a computer screen in relation to the structure coordinates of PAK6KD. This would be followed by manual model building using software such as SYBYL, (Tripos, St. Louis, MO); Insight II (Accelrys, San Diego, CA); and MOE (Chemical Computing Group, Inc., Montreal, Canada). Other appropriate program are described in, for example, Halperin, et al.

[0218]   Useful programs to aid one of skill in the art in connecting the individual chemical groups or fragments include, for example:

1.   CAVEAT (Bartlett *et al.*, 'CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules'. In Molecular Recognition in Chemical and Biological Problems', Special Pub., *Royal Chem. Soc.* 78:182-96, 1989). CAVEAT is available from the University of California, Berkeley, CA.

2.   3D Database systems such as ISIS or MACCS-3D (MDL Information Systems, San Leandro, Calif.). This area is reviewed in Martin, *J. Med. Chem.* 35:2145-54, 1992).

3.   HOOK (Eisen *et al.*, Proteins: Struct., Funct., Genet., 19:199-221, 1994) (available from Accelrys, Inc., San Diego, CA).

4.   LUDI (Bohm, J. Comp. Aid. Molec. Design 6:61-78, 1992). LUDI is available from Accelrys, Inc., San Diego, CA.

[0219]   Instead of proceeding to build a PAK6 inhibitor in a step-wise fashion one fragment or chemical group at a time, as described above, PAK6 binding compounds may be designed as a whole or 'de novo' using either an empty active site or optionally including some portion(s) of a known inhibitor(s). These methods include, for example:

1.   LUDI (Bohm, J. Comp. Aid. Molec. Design 6:61-78, 1992). LUDI is available from Accelrys, Inc., San Diego, CA.

2.   LEGEND (Nishibata & Itai, Tetrahedron, 47:8985, 1991). LEGEND is available from Accelrys, Inc., San Diego, CA.

3.   LeapFrog (available from Tripos, Inc., St. Louis, Mo.).

4.   SPROUT (Gillet *et al.*, J. Comput. Aided Mol. Design 7:127-53, 1993) (available from the University of Leeds, U.K.).

5.   GenStar (Murcko, M.A. and Rotstein, S.H. J. Comput. Aided Mol. Des. 7:23-43, 1993).

6.   GroupBuild (Rotstein, S.H., and Murcko, M.A., J. Med. Chem. 36:1700, 1993).

7.   GrowMol (Rich, D.H. et al., Chimia, 51:45, 1997).

8.   Grow (UpJohn; Moon J, Howe W, Proteins, 11:314-28, 1991).

9.   SmoG (DeWitte, R.S., Abstr. Pap Am Chem. S. 214:6-Comp Part 1, Sept. 7, 1997; DeWitte, R.S. & Shakhnovich, E.I., J. Am. Chem. Soc. 118:11733-44, 1996).

10.   LigBuilder (PDB (www.rcsb.org/pdb); Wang R, Ying G, Lai L, J. Mol. Model. 6: 498-516, 1998).

[0220] Other molecular modeling techniques may also be employed in accordance with this invention. *See, e.g.*, Cohen *et al.*, *J. Med. Chem.* 33:883-94, 1990. *See also*, Navia & Murcko, *Current Opinions in Structural Biology* 2:202-10, 1992; Balbes *et al.*, *Reviews in Computational Chemistry*, 5:337-80, 1994, (Lipkowitz and Boyd, Eds.) (VCH, New York); Guida, *Curr. Opin. Struct. Biol.* 4:777-81, 1994.

[0221] During design and selection of compounds by the above methods, the efficiency with which that compound may bind to PAK6KD may be tested and optimized by computational evaluation. For example, a compound that has been designed or selected to function as a PAK6 inhibitor may occupy a volume not overlapping the volume occupied by the active site residues when the native substrate is bound, however, those of ordinary skill in the art will recognize that there is some flexibility, allowing for rearrangement of the main chains and the side chains. In addition, one of ordinary skill may design compounds that could exploit protein rearrangement upon binding, such as, for example, resulting in an induced fit. An effective PAK6 inhibitor may demonstrate a relatively small difference in energy between its bound and free states (*i.e.*, it must have a small deformation energy of binding and/or low conformational strain upon binding). Thus, the most efficient PAK6 inhibitors should, for example, be designed with a deformation energy of binding of not greater than 10 kcal/mol, for example, not greater than 7 kcal/mol, for example, not greater than 5 kcal/mol and, for example, not greater than 2 kcal/mol. PAK6 inhibitors may interact with the protein in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free compound and the average energy of the conformations observed when the inhibitor binds to the enzyme.

[0222] A compound selected or designed for binding to PAK6KD may be further computationally optimized so that in its bound state it would, for example, lack repulsive electrostatic interaction with the target protein. Non-complementary electrostatic interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the inhibitor and the protein when the inhibitor is bound to it may make a neutral or favorable contribution to the enthalpy of binding.

[0223] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 94, revision C (Frisch, Gaussian, Inc., Pittsburgh, PA. ©1995);

AMBER, version 7 (Kollman, University of California at San Francisco, ©2002); QUANTA/CHARMM (Accelrys, Inc., San Diego, CA, ©1995); Insight II/Discover (Accelrys, Inc., San Diego, CA, ©1995); DelPhi (Accelrys, Inc., San Diego, CA, ©1995); and AMSOL (University of Minnesota) (Quantum Chemistry Program Exchange, Indiana University). These programs may be implemented, for instance, using a computer workstation, as are well known in the art, for example, a LINUX, SGI or Sun workstation. Other hardware systems and software packages will be known to those skilled in the art.

[0224] Once a PAK6KD binding compound has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or chemical groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, *i.e.*, the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. One of skill in the art will understand that substitutions known in the art to alter conformation should be avoided. Such altered chemical compounds may then be analyzed for efficiency of binding to PAK6KD by the same computer methods described in detail above. Methods of structure-based drug design are described in, for example, Klebe, G., J. *Mol. Med.* 78:269-81, 2000); Hol. W.G.J., Angewandte Chemie (Int'l Edition in English) 25:767-852, 1986; and Gane, P.J. and Dean, P.M., *Current Opinion in Structural Biology*, 10:401-04, 2000.

[0225] The present invention also provides means for the preparation of a compound the structure of which has been identified or designed, as described above, as binding PAK6KD or an active site or binding pocket thereof. Where the compound is already known or designed, the synthesis thereof may readily proceed by means known in the art. Alternatively, compounds that match the structure of one or more pharmacophores as described above may be prepared by means known in the art. In an alternative embodiment, the production of a compound may proceed by introduction of one or more desired chemical groups by attachment to an initial compound which binds PAK6KD or an active site or binding pocket thereof and which has, or has been modified to contain, one or more chemical moieties for attachment of one or more desired chemical groups. The initial compound may be viewed as a "scaffold" comprising at least one moiety capable of binding or associating with one or more residues of PAK6KD or an active site or binding pocket thereof.

[0226] The initial compound may be a flexible or rigid "scaffold", optionally containing a linker for introduction of additional chemical moieties. Various scaffold compounds may be used, including, but not limited to, aliphatic carbon chains, pyrrolidinones, sulfonamidopyrrolidinones, cycloalkanonedienes including cyclopentanonedienes, cyclohexanonedienes, and cycloheptanonedienes, carbazoles, imidazoles, benzimidiazoles, pyridine, isoxazoles, isoxazolines, benzoxazinones, benzamidines, pyridinones and derivatives thereof. Other scaffolds are described in, for example, Klebe, G., *J. Mol. Med.* 78: 269-281 (2000); Maignan, S. and Mikol, V., *Curr. Top. Med. Chem.* 1: 161-174 (2001); and U.S. Patent No. 5,756,466 to Bemis *et al.* The scaffold compound used may, for example, be one that comprises at least one moiety capable of binding or associating with one or more residues of PAK6KD or an active site or binding pocket thereof.

[0227] Chemical moieties on the scaffold compound that permit attachment of one or more desired functional chemical groups may undergo conventional reactions by coupling, substitution, and electrophilic or nucleophilic displacement. For example, the moieties may be those already present on the compound or readily introduced. Alternatively, an variant of the scaffold compound comprising the moieties is utilized initially. As a non-limiting example, the moiety may be a leaving group which can readily be removed from the scaffold compound. Various moieties may be used, including but not limited to pyrophosphates, acetates, hydroxy groups, alkoxy groups, tosylates, brosylates, halogens, and the like. In another embodiment of the invention, the scaffold compound is synthesized from readily available starting materials using conventional techniques. (*See e.g.*, U.S. Patent 5,756,466 for general synthetic methods). Chemical groups are then introduced into the scaffold compound to increase the number of interactions with one or more residues of PAK6KD or an active site or binding pocket thereof.

[0228] Because PAK6KD may crystallize in more than one crystal form, the structure coordinates of PAK6KD, or portions thereof, are particularly useful to solve the structure of those other crystal forms of PAK6KD. They may also be used to solve the structure of PAK6KD mutants, PAK6KD co-complexes, or of the crystalline form of any other protein with significant amino acid sequence homology to any functional domain of PAK6KD.

[0229] Homologs or mutants of PAK6KD may, for example, have an amino acid sequence homology to the Homo sapiens amino acid sequence of Fig. 2 of greater than 60%, more preferred proteins have a greater than 70% sequence homology, more preferred

proteins have a greater than 80% sequence homology, more preferred proteins have a greater than 90% sequence homology, and most preferred proteins have greater than 95% sequence homology. A protein domain, region, or binding pocket may have a level of amino acid sequence homology to the corresponding domain, region, or binding pocket amino acid sequence of Homo sapiens of Fig. 2 of greater than 60%, more preferred proteins have a greater than 70% sequence homology, more preferred proteins have a greater than 80% sequence homology, more preferred proteins have a greater than 90% sequence homology, and most preferred proteins have greater than 95% sequence homology. Percent homology may be determined using, for example, a PSI BLAST search, such as, but not limited to version 2.1.2 (Altschul, S.F., et al., Nuc. Acids Rec. 25:3389-3402, 1997).

[0230] One method that may be employed for this purpose is molecular replacement. In this method, the unknown crystal structure, whether it is another crystal form of PAK6KD, a PAK6KD mutant, or a PAK6KD co-complex, or the crystal of some other protein with significant amino acid sequence homology to any functional domain of PAK6KD, may be determined using phase information from the PAK6KD structure coordinates. This method may provide an accurate three-dimensional structure for the unknown protein in the new crystal more quickly and efficiently than attempting to determine such information *ab initio*. In addition, in accordance with this invention, PAK6KD mutants may be crystallized in co-complex with known PAK6KD inhibitors. The crystal structures of a series of such complexes may then be solved by molecular replacement and compared with that of wild-type PAK6KD. Potential sites for modification within the various binding pockets of the protein may thus be identified. A co-crystal may be obtained, for example, by soaking a crystalline form of a target protein in the presence of at least one ligand. Or, a co-crystal may be obtained, for example, by crystallizing a co-complex, by preparing a solution comprising a target protein and a ligand, and then following an appropriate crystallization method. The ligand may be present in the mother liquor or, if it is insoluble in the mother liquor, it may be dissolved, at the highest concentration possible, in DMSO, for example.

[0231] This information provides an additional tool for determining the most efficient binding interactions, for example, increased hydrophobic interactions, between PAK6KD and a chemical group or compound.

[0232]   If an unknown crystal form has the same space group as and similar cell dimensions to the known PAK6KD crystal form, then the phases derived from the known crystal form may be directly applied to the unknown crystal form, and in turn, an electron density map for the unknown crystal form may be calculated. Difference electron density maps can then be used to examine the differences between the unknown crystal form and the known crystal form. A difference electron density map is a subtraction of one electron density map, e.g., that derived from the known crystal form, from another electron density map, e.g., that derived from the unknown crystal form. Therefore, all similar features of the two electron density maps are eliminated in the subtraction and only the differences between the two structures remain. For example, if the unknown crystal form is of a **PAK6KD** co-complex, then a difference electron density map between this map and the map derived from the native, uncomplexed crystal will ideally show only the electron density of the ligand. Similarly, if amino acid side chains have different conformations in the two crystal forms, then those differences will be highlighted by peaks (positive electron density) and valleys (negative electron density) in the difference electron density map, making the differences between the two crystal forms easy to detect. However, if the space groups and/or cell dimensions of the two crystal forms are different, then this approach will not work and molecular replacement must be used in order to derive phases for the unknown crystal form.

[0233]   All of the complexes referred to above may be studied using well-known X-ray diffraction techniques and may be refined against data extending from about 500Å to at least 3.0Å or 1.5Å, until the refinement has converged to limits accepted by those skilled in the art, such as, but not limited to, R=0.2, Rfree=0.25. This may be determined using computer software, such as X-PLOR, CNX, or refmac (part of the CCP4 suite; Collaborative Computational Project, Number 4, "The CCP4 Suite: Programs for Protein Crystallography," Acta Cryst. D50, 760-63, 1994). See, e.g., Blundell et al ., Protein Crystallography, Academic Press; Methods in Enzymology, Vols. 114 & 115, 1976; Wyckoff et al., eds., Academic Press, 1985; Methods in Enzymology, Vols. 276 and 277 (Carter & Sweet, eds., Academic Press 1997); "Application of Maximum Likelihood Refinement" G. Murshudov, A.Vagin and E.Dodson, (1996) in the Refinement of Protein Structures, Proceedings of Daresbury Study Weekend; G.N. Murshudov, A.A.Vagin and E.J.Dodson, Acta Cryst. D53, 240-55, 1997; G.N.Murshudov, A.Lebedev, A.A.Vagin, K.S.Wilson and E.J.Dodson, Acta Cryst. Section D55, 247-55, 1999. See, e.g., Blundell et

al., Protein Crystallography, Academic Press; Methods in Enzymology, Vols. 114 & 115, 1976; Wyckoff *et al.*, eds., Academic Press, Methods in Enzymology, Vols. 276 and 277, 1985 (Carter & Sweet, eds., Academic Press 1997). This information may thus be used to optimize known classes of PAK6 inhibitors, and more importantly, to design and synthesize novel classes of PAK6 inhibitors.

[0234] The structure coordinates of PAK6KD mutants will also facilitate the identification of related proteins or enzymes analogous to PAK6 in function, structure or both, thereby further leading to novel therapeutic modes for treating or preventing diseases or disorders in which PAK6 activity is implicated.

[0235] Subsets of the molecular structure coordinates may be used in any of the above methods. Particularly useful subsets of the coordinates include, but are not limited to, coordinates of single domains, coordinates of residues lining an active site or binding pocket, coordinates of residues that participate in important protein-protein contacts at an interface, and alpha-carbon coordinates. For example, the coordinates of one domain of a protein that contains the active site may be used to design inhibitors that bind to that site, even though the protein is fully described by a larger set of atomic coordinates. Therefore, a set of atomic coordinates that define the entire polypeptide chain, although useful for many applications, do not necessarily need to be used for the methods described herein.

EXAMPLES

Example 1: Determination of PAK6 Structure

[0236] The subsections below describe the production of a polypeptide comprising the Homo sapiens PAK6, and the preparation and characterization of diffraction quality crystals and heavy-atom derivative crystals.

Example 1.1: Preparation of PAK6 Crystals

[0237] Human liver cDNA is synthesized using a standard cDNA synthesis kit following the manufacturers' instructions. The template for the cDNA synthesis is mRNA isolated from JAR cells [ATCC HTB-144] using a standard RNA isolation kit. An open-reading frame for PAK6KD is amplified from the human liver cDNA by the polymerase chain reaction (PCR) using the following primers:

[0238] Forward primer: ACACATGAGCAGTTCAAGG

Reverse primer: CCTTTCGGTAGAGCTGGATC

The PCR product (873 base pairs expected) is electrophoresed on a 1% agarose gel in TBE buffer and the appropriate size band is excised from the gel and eluted using a standard gel extraction kit.

[0239] The eluted DNA is ligated for five minutes at room temperature with topoisomerase into pSGX6, previously digested with BamHI and HindIII. The vector pSGX6 is a topoisomerase-activated modified version of pET26b (Novagen, Madison, Wisconsin) wherein the coding sequence for smt3 (Genbank entry U27233) from amino acids 1 to 121 has been inserted between the NdeI and BamHI sites (Bernier-Villamor, V., et al., Cell 108:345-356, 2002). In addition, the pSGX6 vector contains a gene coding for lambda phosphatase.

[0240] The phosphatase co-expression plasmid was created by inserting the phosphatase gene from lambda bacteriophage into the above plasmid (Matsui T, et al., Biochem. Biophys. Res. Commun., 2001, 284:798-807). The phosphatase gene was amplified using PCR from template lambda bacteriophage DNA (HinDIII digest, New England Biolabs) using the following oligonucleotide primers:

Forward primer (PPfor): GCAGAGATCCGAATTCGAGCTCCGTCGACGGAT GGAGTGAAAGAGATGCGC

Reverse primer (PPrev): GGTGGTGGTGCTCGAGTGCGGCCGCAA GCTTTCATCATGCGCCTTCTCCCTGTAC

[0241] The PCR product (744 base pairs expected) was gel purified. The purified DNA and non-co-expression plasmid DNA were then digested with SacI and XhoI restriction enzymes. Both the digested plasmid and PCR product were then gel purified and ligated together for 8 hrs at 16° C with T4 DNA ligase and transformed into Top10 cells using standard procedures. The presence of the phosphatase gene in the co-expression plasmid was confirmed by sequencing. For standard molecular biology protocols followed here, see also, for example, the techniques described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY, 2001, and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY, 1989.

[0242] The lambda phosphatase/PAK6KD co-expression plasmid contains both the PAK6KD and lambda phosphatase sequences under the control of the lac promoter, each with its own ribosome binding site. By cloning the phosphatase into the middle of the multiple cloning site, downstream of the target gene, convenient restriction sites are

available for subcloning the phosphatase into other plasmids. These sites include SacI, SalI and EcoRI between the kinase and phosphatase and HinDIII, NotI and XhoI downstream of the phosphatase.

[0243] The resulting sequence of the PAK6KD gene after being ligated into the vector, from the Shine-Dalgarno sequence through the stop site and the "original" HindIII, site is as follows: AAGGAGATATA CCATGGGCAGCA GCCATCATCATCATCA TCACAGCAGCGGCCT GGTGCCGCGCGGCAGCCATA TGGCTAGC[SMT3]TCC[ORF]. The PAK6KD expressed using this vector has an N-terminal methionine, then a 6 x His-tag followed by the smt3 fusion protein followed by the kinase domain of PAK6KD.

[0244] Plasmids containing ligated inserts are transformed into chemically competent TOP10 cells. Colonies are then screened for inserts in the correct orientation and small DNA amounts are purified using a "miniprep" procedure from 2 ml cultures, using a standard kit, following the manufacturer's instructions. For standard molecular biology protocols followed here, see also, for example, the techniques described in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY, 2001, and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY, 1989.

[0245] The miniprep DNA is transformed into BL21(DE3)-Codon+RIL cells and plated onto petri dishes containing LB agar with 30 μg/ml of kanamycin and 34 μg/ml of chloramphenicol. Isolated, single colonies are grown to mid-log phase and stored at − 80°C in LB containing 15% glycerol.

[0246] The PAK6KD fusion protein is over expressed in *E. coli* in the presence of 60 mg/L selenomethionine as follows. Glycerol stocks are grown in LB (10g/L tryptone, 5g/L yeast extract, 10g/L NaCl) with 30 μg/ml kanamycin and 34 μg/ml chloramphenicol. The culture is grown to an OD600 of 0.6 to 1.0, then IPTG is added at a 0.4mM final concentration. The culture is allowed to ferment for 16hr at 20°C. The PAK6KD is purified as follows. Cells are collected by centrifugation, lysed in diluted cracking buffer (50 mM Tris HCl, pH 7.6, 0.1% Tween20), and centrifuged to remove cell debris. The soluble fraction is purified over an IMAC column charged with nickel (Pharmacia, Uppsala, Sweden), and eluted under native conditions with a gradient of 20mM to 500mM imidazole in 50mM Tris.pH7.8, 10mM methionine, 10% glycerol. Next, the PAK6KD

fusion protein is mixed with Ulp1 protease at a concentration of 1:10,000 in elution buffer and incubated overnight at 4°C (Bernier-Villamor, V., et al., Cell, 108:345-56, 2002); Mossessova, E., and Lima, C.D., Mol. Cell 5:865-76, 2000). The cleavage reaction takes place during dialysis against the IMAC starting buffer. The cleaved PAK6 fusion protein is passed over an IMAC column, charged with nickel, a second time. The cleaved PAK6 is recovered from the flowthrough, whereas the Smt-fusion partner, the uncleaved protein, and the His-tagged Ulp protease remained bound to the column. The cleaved PAK6KD fusion protein is then further purified by gel filtration using a Superdex 200 preparative grade column equilibrated in GF5 buffer (10mM HEPES, 10mM methionine, 500 mM NaCl, 5 mM DTT, and 10% glycerol). Fractions containing the purified PAK6KD kinase domain are pooled, concentrated to 8.5mg/ml, flash frozen and stored at -80°C. The protein obtained is 99% pure as judged by electrophoresis on SDS polyacrylamide gels. Mass spectroscopic analysis of the purified protein showed that it is predominantly singly phosphorylated.

[0247] For crystals of Homo sapiens PAK6 from which the molecular structure coordinates of the invention are obtained, it has been found that a sitting drop containing 1 µl of PAK6 polypeptide, 14 mg/ml, in 10 mM Hepes pH 7.5, 150 mM NaCl, 5mM DTT 10mM methionine, 1mM ADP, 2mM MgCl$_2$, 10% glycerol, and 1µl reservoir solution: 15 % (v/v) PEG 400, 200 mM sodium citrate dihydrate and 100 mM Tris-HCl, pH 8.5 in a sealed container containing 100µL reservoir solution, incubated at 21°C provides diffraction quality crystals. In one example, crystals first appeared within 24 hours, and matured within about 4 weeks.

[0248]Other examples of methods of obtaining a crystal comprise the steps of:(a) mixing a volume of a solution comprising the PAK6 with a volume of a reservoir solution comprising a precipitant, such as, for example, polyethylene glycol; and (b) incubating the mixture obtained in step (a) over the reservoir solution in a closed container, under conditions suitable for crystallization until the crystal forms. At least 10% (v/v) of PEG 400 is present in the reservoir solution. PEG 400 is, for example, present in a concentration up to about 20% (v/v). In another example, the concentration of PEG 400 is 15% (v/v). The concentration of Tris-HCl is, for example, at least 25mM. The concentration of Tris-HCl is, for example, up to about 200mM. In another example, the concentration of Tris-HCl is 100mM. The concentration of sodium citrate dihydrate is, for

example, at least 100mM. The concentration of sodium citrate dihydrate is, for example, up to about 300mM. In another example, the concentration of sodium citrate dihydrate is 200 mM. The reservoir solution has a pH of, for example, 8. The reservoir solution may, for example, have a pH up to about 9. In another example, the pH is about 8.5. The temperature is, for example, at least 4°C. The temperature may be, for example, up to about 30°C. In another example, the temperature is 21°C.

[0249] Those of ordinary skill in the art recognize that the drop and reservoir volumes may be varied within certain biophysical conditions and still allow crystallization.

Example 1.2: Crystal Diffraction Data Collection

[0250] The crystals are individually harvested from their trays and transferred to a cryoprotectant consisting of 80% reservoir solution plus 20% glycerol. After about 2 minutes the crystal is collected and transferred into liquid nitrogen. The crystals are transferred in liquid nitrogen to the Advanced Photon Source (Argonne National Laboratory) where a native data set is collected.

Example 1.3: Structure Determination

[0251] X-ray diffraction data are indexed and integrated using the program MOSFLM (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994; www.ccp4.ac.uk/main.html) and then merged using the program SCALA (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994; www.ccp4.ac.uk/main.html). The subsequent conversion of intensity data to structure factor amplitudes is carried out using the program TRUNCATE (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-763, 1994; www.ccp4.ac.uk/main.html). An initial model was obtained by molecular replacement using a structure of PAK4, for example, a structure having the coordinates of a structure described in Publication No. US-2003-0229453-A1, published on December 11, 2003. as a search model using the program EPMR (Kissinger, CR, et al., *Acta Cryst.*, D55, 484-491, 1999). The initial protein model was built into the resulting map using the program XTALVIEW/XFIT (McRee, D.E. *J. Structural Biology*, 125:156-65, 1993; available from CCMS (San Diego Super Computer Center) CCMS-request@sdsc.edu.).

[0252]   This model is refined using the program REFMAC (Brunger et al., Acta Cryst. D53, 240-55, 2000; Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994; www.ccp4.ac.uk/main.html) with interactive refitting carried out using the program XTALVIEW/XFIT (McRee, D.E. *J. Structural Biology,* 125:156-65, 1993; available from CCMS (San Diego Super Computer Center) CCMS-request@sdsc.edu). The stereochemical quality of the atomic model is monitored using PROCHECK (Laskowski et al., *J. Appl. Cryst.* 26, 283-91, 1993) and WHATCHECK (Vriend, G., *J. Mol. Graph* 8:52-56, 1990; Hooft, R.W.W. et al., *Nature* 381:272, 1996) and the agreement of the model with the x-ray data is analyzed using SFCHECK (Collaborative Computational Project, Number 4, *Acta. Cryst.* D50, 760-63, 1994); www.ccp4.ac.uk/main.html).

Table 1 Data Collection Statistics

Space group	P 21 21 21
Cell dimensions	$a = 59.24$ Å
	$b = 66.72$ Å
	$c = 97.21$ Å
	$\alpha = 90°$
	$\beta = 90°$
	$\gamma = 90°$
Wavelength λ	0.9794 Å
Overall Resolution limits	21.6 Å
	1.46 Å
Number of reflections collected	241955
Number of unique reflections	64186
Overall Redundancy of data	3.6
Overall Completeness of data	98.4 %
Completeness of data in last data shell	90.9 %
Overall R_{SYM}	0.124
R_{SYM} in last resolved shell	1.793
Overall I/sigma(I)	6.4
I/sigma(I) in last shell	1.0

Table 2 Model Refinement Statistics

Model		
	Total number of atoms	2631
	Number of water molecules	240
	Temperature factor for all atoms	17.8 $Å^2$
	Matthews coefficient	2.61

	Corresponding solvent content	52.5 %
Refinement		
	Resolution limits	21.6 Å 1.46 Å
	Number of reflections used	64131
	with I > 1 sigma(I)	62900
	with I > 3 sigma(I)	32421
	Completeness	95 %
	R-factor for all reflections	0.196
	Correlation coefficient	0.955
	Number of reflections above 2 sigma(F) and resolution from 5.0 Å - high resolution limit	61215
	used to calculate Rworking	58117
	used to calculate Rfree	3098
	R-factor without free reflections	0.190
	R-factor for free reflections	0.224
	Error in coordinates estimated by Luzzati plot	0.187 Å
Validation		
	Phi-Psi core region	93.1 %
	Phi-Psi violations Residues in disallowed regions:	1
% bad contacts	Short contact distances	0
	RMSD from ideal bond length	0.021 Å
	RMSD from ideal bond angle	1.88 °

Example 1.4: Structure Analyses

[0253]   Atomic superpositions are performed with MOE (available from Chemical Computing Group, Inc., Montreal, Quebec, Canada). Per residue solvent accessible surface calculations are done with GRASP (Nicholls *et al.*, "Protein folding and association: insights from the interfacial and thermodynamic properties of hydrocarbons," Proteins, 11:281-96, 1991). The electrostatic surface is calculated using a probe radius of 1.4Å.

Example 2: Use of PAK6KD Coordinates for Inhibitor Design

[0254]   The coordinates of the present invention, including the coordinates of molecules comprising the binding pocket residues of Figure 4, as well as coordinates of homologs having a rmsd of the backbone atoms of preferably less than 1.5Å, more preferably less than 1.25Å, more preferably less than 1Å, more preferably less than 0.75Å, and more

preferably less than 0.5Å from the coordinates of Figure 4, are used to design compounds, including inhibitory compounds, that associate with PAK6, or homologs of PAK6. Such compounds may associate with PAK6 at the active site, in a binding pocket, in an accessory binding pocket, or in parts or all of both regions.

[0255] The process may be aided by using a computer comprising a computer readable database, wherein the database comprises coordinates of an active site, binding pocket, or accessory binding pocket of the present invention. The computer may be programmed, for example, with a set of machine-executable instructions, wherein the recorded instructions are capable of displaying a three-dimensional representation of PAK6, or portions thereof. The computer is used according to the methods described herein to design compounds that associate with PAK6, for example, at the active site or a binding pocket.

[0256] A chemical compound library is obtained. The library may be purchased from a publicly available source such as, for example, ChemBridge (San Diego, California, www.chembridge.com), Available Chemical Database, or Asinex (Moscow 123182, Russia, www.asinex.com). A filter is used to retain compounds in the library that satisfy the Lipinski rule of five, which states that compounds are likely to have good absorption and permeation in biological systems and are more likely to be successful drug candidates if they meet the following criteria: five or fewer hydrogen-bond donors, ten or fewer hydrogen-bond acceptors, molecular weight less than or equal to 500, and a calculated logP less than or equal to 5. (Lipinski, C.A., et al., Advanced Drug Delivery Reviews 23 3-25 (1996)).

[0257] This filter reduces the size of the compound library used to screen against the structure of the present invention. Docking programs described herein, such as, for example, DOCK, or GOLD, are used to identify compounds that bind to the active site and/or binding pocket. Compounds may be screened against more than one binding pocket of the protein structure, or more than one set of coordinates for the same protein, taking into account different molecular dynamic conformations of the protein. Consensus scoring may then be used to identify the compounds that are the best fit for the protein (Charifson, P.S. et al., J. Med. Chem. 42:5100-9 (1999)). Data obtained from more than one protein molecule structure may also be scored according to the methods described in Klingler et al., U.S. Utility Application, filed May 3, 2002, entitled "Computer Systems and Methods for Virtual Screening of Compounds." Compounds having the best fit are

then obtained from the producer of the chemical library, or synthesized, and used in binding assays and bioassays.

[0258] The coordinates of the present invention are also used to determine pharmacophores. These pharmacophores may be designed after reviewing results from the use of a docking program, to determine the shape of the PAK6 pharmacophore. Alternatively, programs such as GRID are used to calculate the properties of a pharmacophore. Once the pharmacophore is determined, it may be used to screen chemical libraries for compounds that fit within the pharmacophore.

[0259] The coordinates of the present invention are also used to identify substructures that interact with various portions of an active site or binding pocket of PAK6. Once a substructure, or set of substructures, is determined, it is used to screen a chemical library for compounds comprising the substructure or set of substructures. The identified compounds are then docked to, for example, the active site or binding pocket.

Example 3: Bioassay

[0260] The kinase assays may use various forms of PAK6KD and PAK6, including, for example, PAK6KD or the PAK6 molecule itself, or a portion thereof.

Binding Assay:

[0261] To measure the binding of a compound to PAK6 or PAK6KD, a test kit manufactured by Discoverx (Fremont, CA), ED-Staurosporine NSIP™ Enzyme Binding Assay Kit (see U.S. Patent No. 5,643,734) is used.

PAK4 Kinase assay:

[0262] To assay the kinase activity of PAK6 or PAK6KD, NIH 3T3 cells are transfected with either empty SRα expression vector or expression vectors containing HA-tagged PAK6 or PAK6KD. Cells are harvested in M2 buffer (Minden, A. *et al.,Science*, 266:1719-23, 1994) 48 h after transfection. Approximately 100 μg of cell extracts are mixed with anti-HA antibody and protein A-Sepharose and incubated 2 h to overnight at 4°C. The immune complexes are washed twice with M2 buffer and twice in 20 mM HEPES, pH 7.5, and incubated in a kinase buffer containing 20 μM ATP and 5 μCi of [γ-^{32}P]ATP together with either 5 μg of histone H4 or MBP (Boehringer Mannheim) or no substrate, at 30°C for 20 min. The reaction is stopped by boiling in 4× SDS loading buffer.

Proteins are resolved by SDS-PAGE, and substrate phosphorylation and autophosphorylation are visualized by autoradiography.

[0263] To measure autophosphorylation of purified PAK6 or PAK6KD, recombinant PAK6 or PAK6KD (2 μg bound to protein G-Sepharose conjugated with monoclonal glu-glu antibody) is washed once and incubated in 40 μl of kinase buffer (50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 10 mM MgCl$_2$, 1 mM MnCl$_2$) with 2 μg of either Rac1 or Cdc42Hs, all previously loaded with GTP or GDP. The reaction is initiated by adding 10 μl of kinase buffer containing 50 μM ATP and 5 μCi of [γ-^{32}P]ATP and incubated for 20 min at 30°C. The reaction is stopped by adding 10 μl of 5× SDS-PAGE sample buffer and boiling for 5 min. Samples are applied to a 14% SDS-PAGE gel and exposed to film.

[0264] To measure modulation, activation, or inhibition of PAK6 or PAK6KD kinase activity, a test compound is added to the assay at a range of concentrations. Inhibitors may, for example, inhibit PAK6 or PAK6KD activity at an IC_{50} under 100 μM, for example under 10 μM, for example, under 1 μM, in the nanomolar range, or, for example, in the sub-nanomolar range.

Apoptosis Assay:

[0265] The ability of PAK6 or PAK6KD to protect cells against apoptosis and delay caspase activation is measured as described (Gnesutta, N., et al., J. Biol. Chem., 276: 14414-19, 2001). NIH3T3 cells are stably transfected with either control, wild-type, or mutant PAK6 or PAK6KD vector (Qu, J. et al., Mol Cell Biol, 10: 3523-33, 2001). To estimate the level of apoptosis and survival of stably transfected cell lines, equal numbers of cells are seeded in growth medium in 3.5-, 6-, or 10-cm plates. After 48 hours, cells are assayed for apoptosis induction following treatments with UV irradiation, tumor necrosis factor alpha (TNFα), and serum deprivation. For UV irradiation, cells are washed twice in phosphate-buffered saline (PBS). After removal of the PBS, cells are exposed to 50 J/m^2 UV-light in a UV cross-linker (Fisher) followed by addition of fresh medium. For TNFα treatment, cells are washed once with fresh medium that was replaced by medium containing TNFα and cycloheximide (CHX) either alone or in combination at a concentration of 10 ng/ml and 10 μg/ml, respectively (CHX is used as a control to block the NF-kB-mediated survival pathway induced by TNFα). For serum deprivation experiments, cells are washed once with medium without serum, followed by addition of

fresh medium containing 0.1, 0.5, or 10% serum for 24 h. After stimulation, cells are collected at 1 h, 2 h, and 4 h intervals and fixed for flow cytometry analysis or used to prepare total cell extracts. To determine the percentage of cell death by flow cytometry analysis, cells with DNA content lower than the G_1 peak (sub-G_1) are considered to be apoptotic. Caspase-3-like activity is examined by Western blot analysis of the caspase-3 substrate PARP in equal amounts of cell lysate. Detection of the M_r 85,000 proteolytic product of PARP is used as an indication of caspase activity. To examine nuclear condensation, cells stained with Hoechst 33258 are analyzed by fluorescence microscopy. Cells that displayed condensed chromatin and blebbed nuclei are considered apoptotic. To determine the amount of cell death in each clone, apoptotic cells are counted in the same number of viewing fields. To determine survival rates, cells are seeded in 6-well plates and treated as described above. At the indicated time point, the medium is aspirated, and floating cells are removed by washing twice with PBS. Attached cells are collected and counted. The survival rate is expressed in percentage of surviving cells in treated cells compared with the untreated control.

[0266]   To measure modulation, activation, or inhibition of PAK6KD, a test compound is added to the assay at a range of concentrations. Inhibitors may inhibit PAK6KD activity at an IC_{50} in the nanomolar range, and, for example, in the subnanomolar range.

[0267]   To measure modulation, activation, or inhibition of PAK6KD, a test compound is added to the assay at a range of concentrations. Preferred inhibitors inhibit PAK6KD activity at an IC_{50} in the nanomolar range, or in the subnanomolar range.

Example 4: Formulation and Administration

[0268]   Pharmaceutical compositions comprising PAK6 modulators, such as inhibitors, are useful, for example, for treating diseases and conditions that may be alleviated by modulation of PAK6. Pharmaceutical compositions containing PAK6 effectors may also be used to modify the activity of human homologs of PAK6.

[0269]   In therapeutic and/or diagnostic applications, the compounds of the invention may be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

[0270] The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg from 0.5 to 100 mg, and from 1 to 50 mg per day, from 5 to 40 mg per day are examples of dosages that may be used. One example of a dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0271] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[0272] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained- low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

[0273] For injection, the agents of the invention may be formulated in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants

appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds may be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[0274]   Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0275]   In addition to the active ingredients, these pharmaceutical compositions **may** contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which may be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[0276]   Pharmaceutical preparations for oral use may be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0277]   Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc,

polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0278]   Pharmaceutical preparations that may be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0279]   The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those having skill in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the invention. References cited throughout this application are examples of the level of skill in the art and are hereby incorporated by reference herein in their entirety, whether previously specifically incorporated or not.

1.   A PAK6or PAK6KD protein, or a functional PAK6KD protein subunit, in crystalline form.

2.   The crystalline protein or functional protein subunit of claim 1, which is a heavy-atom derivative crystal.

3.   The crystalline protein or functional protein subunit of claim 2, in which PAK6KD protein is a mutant.

4.   The crystalline protein of claim 3, which is characterized by a set of structural coordinates that is substantially similar to the set of structural coordinates of Fig. 4.

5. A crystal comprising PAK6 protein and a ligand.

6. A method of identifying a ligand that binds PAK6 protein, comprising;
   a)   forming a co-crystal of a test ligand and PAK6 protein;
   b)   analyzing said co-crystal using X-ray crystallography; and
   c)   using said analysis to determine whether said test ligand binds PAK6 protein.

7. The method of claim 6 wherein said co-crystal is obtained by soaking a PAK6 protein crystal in a solution comprising said test ligand.

8. The method of claim 7 wherein said co-crystal is obtained by co-crystallizing PAK6 protein in the presence of said test ligand.

9.   A machine-readable medium embedded with information that corresponds to a three-dimensional structural representation of a crystalline protein of claim 1.

10.   The machine-readable medium of claim 9, embedded with the molecular structural coordinates of Fig. 4, or at least 50% of the coordinates thereof.

11. The machine-readable medium of claim 9, embedded with the molecular structural coordinates of Fig. 4, or at least 80% of the coordinates thereof.

12. The machine-readable medium of claim 9, embedded with the molecular structural coordinates of a protein molecule comprising a PAK6KD protein binding pocket, wherein said binding pocket comprises at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 having the structural coordinates of Fig. 4, or by the structural coordinates of a binding pocket homolog, wherein said the root mean square deviation of the backbone atoms of the amino acid residues of said binding pocket and said binding pocket homolog is less than 2.0Å.

13. The machine-readable medium of claim 12, wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

14. The machine-readable medium of claim 13, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

15. The machine-readable medium of claim 14, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

16. A method of electronically transmitting all or part of the information stored in the machine-readable medium of claim 9.

17. A method of producing a computer readable database comprising the three-dimensional molecular structural coordinates of a binding pocket of a PAK6KD protein, said method comprising

a)   obtaining three-dimensional structural coordinates defining said protein or a binding pocket of said protein, from a crystal of said protein; and

b)   introducing said structural coordinates into a computer to produce a database containing the molecular structural coordinates of said protein or said binding pocket.

18.   The method of claim 17, wherein said binding pocket of said protein is part of a co-complex with at least one ligand.

19.   The method of claim 17 wherein said binding pocket comprises amino acids Val, Lys, Glu, Val, Met, Glu, Leu, Leu, Ser, and Asp.

20.   The method of claim 19 wherein said computer is capable of utilizing or displaying a three-dimensional molecular structure comprising said binding pocket using said structural coordinates.

21.   The method of claim 19 wherein said binding pocket further comprises amino acids corresponding to Gly, Glu, Gly, Ser, Thr, Gly, Ile, Ala, Met, Phe, and Asp.

22.   The method of claim 21 wherein said binding pocket further comprises amino acids corresponding to Leu, Gln, Arg, Leu, Gln, Gly, Gly, Ala, Asp, Gly, Phe, Arg, and Lys.

23.   The method of claim 17 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

24.   The method of claim 23 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

25.   The method of claim 24, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

26.   The method of claim 25, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

27.   The method of claim 17, wherein said binding pocket comprises an active site.

28.   A computer readable database produced by claim 17.

29.   A method comprising electronic transmission of all or part of the computer readable database produced by claim 17.

30.   A method of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of a PAK6KD protein, said method comprising

a)   introducing into a computer program a computer readable database produced by claim 17;

b)   generating a three-dimensional representation of a binding pocket of said PAK6KD protein in said computer program;

c)   superimposing a three-dimensional model of at least one binding test compound on said representation of the binding pocket;

d)   assessing whether said test compound model fits spatially into the binding pocket of said PAK6KD protein; and

e)   storing a representation of a compound that fits into the binding pocket into a computer readable database.

31.   The method of claim 30 wherein in e), said representation is stored in the database produced by claim 17.

32. The method of claim 30, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

33. The method of claim 30, wherein said generating of a three-dimensional representation of the binding pocket comprises use of structural coordinates having a root mean square deviation of the backbone atoms of the amino acid residues of said binding pocket of less than 2.0Å from the structural coordinates of the corresponding residues according to Fig. 4.

34. The method of claim 30, wherein said at least one binding test compound is selected by a method selected from i) selecting a compound from a small molecule database, (ii) modifying a known inhibitor, substrate, reaction intermediate, or reaction product, or a portion thereof, of PAK6KD, (iii) assembling chemical fragments or groups into a compound, and (iv) de novo ligand design of said compound.

35. The method of claim 30, wherein said assessing of whether a test compound model fits is by docking the model to said representation of said PAK6KD binding pocket and/or performing energy minimization.

36. The method of claim 30 further comprising

f) preparing a binding test compound represented in said computer readable database;

g) contacting said compound in a binding assay with a protein comprising said PAK6KD protein binding pocket;

h) determining whether said test compound binds to said protein in said assay; and

i) introducing a representation of a compound that binds to said protein in said assay into a computer readable database.

37.   The method of claim 35 wherein in i), said representation is stored in said database.

38.   The method of claim 35, wherein said representation is selected from the group consisting of the compound's name, a chemical formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

39.   A method of producing a computer readable database comprising a representation of a binding pocket of a PAK6KD protein in a co-crystal with a compound, said method comprising

a)   preparing a binding test compound represented in a computer readable database produced by claim 30;

b)   forming a co-crystal of said compound with a protein comprising a binding pocket of a PAK6KD protein;

c)   obtaining the structural coordinates of said binding pocket in said co-crystal; and

d)   introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database.

40.   The method of claim 39, further comprising introducing the structural coordinates of said compound in said co-crystal into said database.

41.   The method of claim 30 wherein said binding pocket comprises amino acids Val, Lys, Glu, Val, Met, Glu, Leu, Leu, Ser, and Asp.

42.   The method of claim 41 wherein said computer is capable of utilizing or displaying a three-dimensional molecular structure of said binding pocket using said structural coordinates.

43.   The method of claim 42 wherein said binding pocket further comprises amino acids corresponding to Gly, Glu, Gly, Ser, Thr, Gly, Ile, Ala, Met, Phe, and Asp.

44. The method of claim 43 wherein said binding pocket further comprises amino acids corresponding to Leu, Gln, Arg, Leu, Gln, Gly, Gly, Ala, Asp, Gly, Phe, Arg, and Lys.

45. The method of claim 30 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

46. The method of claim 45 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

47. The method of claim 46, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

48. The method of claim 47, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

49. The method of claim 30, wherein said binding pocket comprises an active site.

50. A computer readable database produced by claim 30.

51. A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 17.

52. A method of modulating PAK6KD protein activity comprising contacting said PAK6KD with a compound, wherein said compound is represented in a database produced by the method of claim 30.

53. A method of producing a compound comprising a three-dimensional molecular structure represented by the coordinates contained in a computer readable database produced by claim 30 comprising synthesizing said compound wherein said compound binds in a binding pocket of PAK6KD protein.

54. A method of modulating PAK6KD protein activity, comprising contacting said PAK6KD protein with a compound produced by claim 53.

55. A method of identifying an activator or inhibitor of a protein that comprises a PAK6KD active site or binding pocket, comprising

a) producing a compound according to claim 53;

b) contacting said compound with a protein that comprises a PAK6KD active site or binding pocket; and

c) determining whether the potential modulator activates or inhibits the activity of said protein.

56. A method of producing an activator or inhibitor identified by claim 55.

57. A method of producing a computer readable database comprising a representation of a compound rationally designed to be capable of binding a binding pocket of a PAK6KD protein, said method comprising

a) introducing into a computer program a computer readable database produced by claim 17;

b) generating a three-dimensional representation of the protein or a binding pocket of said PAK6KD protein in said computer program;

c) designing a three-dimensional model of a compound that forms non-covalent bonds with amino acids of a binding pocket of said representation; and

d) storing a representation of said compound into a computer readable database.

58.   The method of claim 58, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional structural coordinates of the compound.

59.   The method of claim 57 further comprising

e)   preparing a binding test compound comprising a three-dimensional molecular structure represented by the coordinates contained in said computer readable database;

f)   contacting said compound in a binding assay with a protein comprising said binding pocket of a PAK6KD protein;

g)   determining whether said test compound binds to said protein in said assay; and

h)   introducing a representation of a compound that binds to said protein in said assay into a computer-readable database.

60.   The method of claim 59, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional structural coordinates of the compound.

61.   A method of producing a computer readable database comprising a representation of a binding pocket of a PAK6KD protein in a co-crystal with a compound rationally designed to be capable of binding said binding pocket, said method comprising

a)   preparing a binding test compound represented in a computer readable database produced by claim 57;

b)   forming a co-crystal of said compound with a protein comprising a binding pocket of a PAK6KD protein;

c)   obtaining the structural coordinates of said binding pocket in said co-crystal; and

d)   introducing the structural coordinates of said binding pocket or said co-crystal into a computer-readable database.

62.   The method of claim 61, further comprising introducing the structural coordinates of said compound in said co-crystal into said database.

63.   The method of claim 57 wherein said binding pocket comprises amino acids Val, Lys, Glu, Val, Met, Glu, Leu, Leu, Ser, and Asp.

64.   The method of claim 63 wherein said binding pocket further comprises amino acids corresponding to Gly, Glu, Gly, Ser, Thr, Gly, Ile, Ala, Met, Phe, and Asp.

65.   The method of claim 64 wherein said binding pocket further comprises amino acids corresponding to Leu, Gln, Arg, Leu, Gln, Gly, Gly, Ala, Asp, Gly, Phe, Arg, and Lys.

66.   The method of claim 57 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

67.   The method of claim 66 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

68.   The method of claim 67, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

69.   The method of claim 68, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

70.   The method of claim 57, wherein said binding pocket comprises an active site.

71.   A computer readable database produced using the method of claim 57.

72   A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 57.

73   A method of producing a computer readable database comprising structural information about a molecule or a molecular complex of unknown structure comprising:

a)   generating an x-ray diffraction pattern from a crystallized form of said molecule or molecular complex;

b)   using a molecular replacement method to interpret the structure of said molecule; wherein said molecular replacement method uses the structural coordinates of a crystalline protein of claim 1, or the structural coordinates of Fig. 4, or a subset thereof comprising a binding pocket, the structural coordinates of a binding pocket of Fig. 4, or structural coordinates having a root mean square deviation for the alpha-carbon atoms of said structural coordinates of less than 2.0Å; and

c)   storing the coordinates of the resulting structure in a computer readable database.

74.   The method of claim 73 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

75.   The method of claim 74 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

76.   The method of claim 75, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.   .

77.   The method of claim 76, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

78.   The method of claim 73, wherein said binding pocket comprises an active site.

79.   A computer readable database produced using the method of claim 73.

80.   A method comprising electronic transmission of all or part of the computer readable database produced by claim 73.

81.   A method for homology modeling the structure of a PAK6KD protein homolog comprising:

        a)   aligning the amino acid sequence of a PAK6KD protein homolog with an amino acid sequence of PAK6KD protein;

        b)   incorporating the sequence of the PAK6KD protein homolog into a model of the structure of PAK6KD protein, wherein said model has the same structural coordinates as the structural coordinates of a crystalline protein of claim 1, or the structural coordinates of Fig. 4, or wherein the structural coordinates of said model's alpha-carbon atoms have a root mean square deviation from the structural coordinates of Fig. 4, of less than 2.0Å to yield a preliminary model of said homolog;

        c)   subjecting the preliminary model to energy minimization to yield an energy minimized model; and

        d)   remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of said homolog.

82.   A method for identifying a compound that binds PAK6KD protein comprising:

a)   providing a computer modeling program with a set of structural coordinates or a three dimensional conformation for a molecule that comprises a binding pocket of a crystalline protein of claim 1, or a homolog thereof;

b)   providing a said computer modeling program with a set of structural coordinates of a chemical entity;

c)   using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket; and

d)   determining whether said chemical entity potentially binds to or interferes with said protein or homolog.

83.   The method of claim 82 further comprising the steps of:

e)   computationally modifying the structural coordinates or three dimensional conformation of said chemical entity to improve the likelihood of binding to said binding pocket; and

b)   determining whether said modified chemical entity potentially binds to or interferes with said protein or homolog.

84.   The method of claim 82 wherein determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket of the protein or homolog; and computationally analyzing the results of the fitting operation to quantify the association between, or the interference with, the chemical entity and the binding pocket.

85.   The method of claim 82 wherein a library of structural coordinates of chemical entities is used to identify a compound that binds.

86.   A method for designing a compound that binds PAK6KD protein comprising:

a)   providing a computer modeling program with a set of structural coordinates, or a three dimensional conformation derived therefrom, for a molecule that comprises a binding pocket comprising the structural coordinates of a binding pocket of a crystalline protein of claim 1, or a homolog thereof;

b)   computationally building a chemical entity represented by set of structural coordinates; and

c)   determining whether the chemical entity is expected to bind to said molecule.

87.   The method of claim 86, wherein determining whether the chemical entity potentially binds to said molecule comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule; and

computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

88.   The method of claim 86 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

89.   The method of claim 88 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

90.   The method of claim 89, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

91.   The method of claim 90, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

92. The method of claim 86, wherein said binding pocket comprises an active site.

93. A method of producing a mutant PAK6KD protein, having an altered property relative to PAK6KD protein, comprising,

a) constructing a three-dimensional structure of PAK6KD protein having structural coordinates selected from the group consisting of the structural coordinates of a crystalline protein of claim 1, the structural coordinates of Fig. 4, and the structural coordinates of a protein having a root mean square deviation of the alpha carbon atoms of said protein of less than 2.0 Å when compared to the structural coordinates of Fig. 4;

b) using modeling methods to identify in the three-dimensional structure at least one structural part of the PAK6KD protein molecule wherein an alteration in said structural part is predicted to result in said altered property;

c) providing a nucleic acid molecule coding for a PAK6KD mutant protein having a modified sequence that encodes a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said structural part; and

d) expressing said nucleic acid molecule to produce said mutant; wherein said mutant has at least one altered property relative to the parent.

94. A method of producing a mutant PAK6KD protein, having an altered property relative to PAK6KD protein, comprising,

a) constructing a three-dimensional structure of a molecule comprising a binding pocket, wherein said binding pocket comprises at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530 , Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 having the structural coordinates of a crystalline protein of claim 1, the structural coordinates of Fig. 4, or the structural coordinates of a binding pocket homolog, wherein said the root mean square deviation of the backbone atoms of the amino acid residues of said binding pocket and said binding pocket homolog is less than 2.0Å;

b) using modeling methods to identify in the three-dimensional structure at least one portion of said binding pocket wherein an alteration in said portion is predicted to result in said altered property;

c)   providing a nucleic acid molecule coding for a mutant PAK6KD protein having a modified sequence that encodes a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said portion; and

d)   expressing said nucleic acid molecule to produce said mutant; wherein said mutant has at least one altered property relative to the parent.

95.   A method of producing a computer readable database containing the three-dimensional molecular structural coordinates of a compound capable of binding the active site or binding pocket of a protein molecule, said method comprising

a)   introducing into a computer program a computer readable database produced by claim 17;

b)   generating a three-dimensional representation of the active site or binding pocket of said PAK6KD protein in said computer program;

c)   superimposing a three-dimensional model of at least one binding test compound on said representation of the active site or binding pocket;

d)   assessing whether said test compound model fits spatially into the active site or binding pocket of said PAK6KD protein;

e)   assessing whether a compound that fits will fit a three-dimensional model of another protein, the structural coordinates of which are also introduced into said computer program and used to generate a three-dimensional representation of the other protein; and

f)   storing the three-dimensional molecular structural coordinates of a model that does not fit the other protein into a computer readable database.

96.   A method for determining whether a compound binds PAK6KD protein, comprising,

a)   providing a computer modeling program with a set of structural coordinates or a three dimensional conformation for a molecule that comprises a binding pocket of a crystalline protein of claim 1, PAK6KD protein, or a homolog thereof;

b)   providing a said computer modeling program with a set of structural coordinates of a chemical entity;

c)   using said computer modeling program to evaluate the potential binding or interfering interactions between the chemical entity and said binding pocket; and

d)   determining whether said chemical entity potentially binds to or interferes with said protein or homolog.

97.   A method of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of a PAK6KD protein, said method comprising,

a)   introducing into a computer program a computer readable database produced by claim 17;

b)   determining a pharmacophore that fits within said binding pocket;

c)   computationally screening a plurality of compounds to determine which compound(s) or portion(s) thereof fit said pharmacophore; and

d)   storing a representation of said compound(s) or portion(s) thereof into a computer readable database.

98.   The method of claim 97, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

99.   The method of claim 97 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

100.   The method of claim 99 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

101.   The method of claim 100, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

102. The method of claim 101, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

103. The method of claim 97, wherein said binding pocket comprises an active site.

104. A computer readable database produced using the method of claim 97.

105. A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 97.

106. A method of producing a computer readable database comprising a representation of a compound capable of binding a binding pocket of a PAK6KD protein, said method comprising

a) introducing into a computer program a computer readable database produced by claim 17;

b) determining a chemical moiety that interacts with said binding pocket;

c) computationally screening a plurality of compounds to determine which compound(s)comprise said moiety as a substructure of said compound(s); and

d) storing a representation of said compound(s) that comprise said substructure into a computer readable database.

107. The method of claim 106, wherein said representation is selected from the group consisting of the compound's name, a chemical or molecular formula of the compound, a chemical structure of the compound, an identifier for the compound, and three-dimensional molecular structural coordinates of the compound.

108. The method of claim 106 wherein said binding pocket comprises a binding pocket defined by the structural coordinates of at least three amino acids selected from the group consisting of Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, Asp544, Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, Asp530, Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676.

109.   The method of claim 108 wherein said binding pocket comprises Val421, Lys436, Glu452, Val465, Met481, Glu482, Leu484, Leu533, Ser543, and Asp544 according to the sequence of Fig. 4.

110.   The method of claim 109, wherein said binding pocket further comprises Gly414, Glu415, Gly416, Ser417, Thr418, Gly419, Ile420, Ala434, Met438, Phe483, and Asp530 according to the sequence of Fig. 4.

111.   The method of claim 110, wherein said binding pocket further comprises Leu423, Gln443, Arg445, Leu449, Gln485, Gly486, Gly487, Ala488, Asp491, Gly546, Phe547, Arg675, and Lys676 according to the sequence of Fig. 4.

112.   The method of claim 106, wherein said binding pocket comprises an active site.

113.   A computer readable database produced using the method of claim 106.

114.   A method comprising electronic transmission of all or part of the computer readable database produced using the method of claim 106.

115.   Crystallizable PAK6 protein.

116.   A method of purifying PAK6 protein linked to a histidine tag comprising:
    a)   obtaining a translation vector comprising a coding sequence for PAK6 protein, linked to a histidine tag;
    b)   performing size exclusion chromatography; and
    c)   performing nickel chelating column chromatography.

117.   Purified PAK6KD polypeptide.

118.   The method of claim 117 wherein said polypeptide is 98% pure.

119.   The method of claim 117 wherein said polypeptide is unphosphorylated.

120. A method of purifying PAK6 polypeptide, comprising

expressing PAK6 in insect cells;

obtaining a soluble protein fraction from said insect cells;

using a two column chromatograph procedure to obtain purified PAK6.

121. An insect cell capable of expressing PAK6.

122. The insect cell of claim 121, wherein said insect cell comprises a vector, wherein said vector comprises a nucleic acid sequence coding for PAK6.

123. The use of the methods of any of claims 6-122 for drug discovery.

ABSTRACT

The present invention provides machine readable media embedded with the three-dimensional molecular structure coordinates of PAK6KD and subsets thereof, including binding pockets, methods of using the structure to identify and design affecters, including inhibitors and activator, mutants of PAK6KD, PAK6KD crystals and compounds and compositions that affect PAK6 activity.

FIG. 1

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SEQRES    1 A   295    SER LEU THR HIS GLU GLN PHE LYS ALA ALA LEU ARG MET
SEQRES    2 A   295    VAL VAL ASP GLN GLY ASP PRO ARG LEU LEU LEU ASP SER
SEQRES    3 A   295    TYR VAL LYS ILE GLY GLU GLY SER THR GLY ILE VAL CYS
SEQRES    4 A   295    LEU ALA ARG GLU LYS HIS SER GLY ARG GLN VAL ALA VAL
SEQRES    5 A   295    LYS MET MET ASP LEU ARG LYS GLN GLN ARG ARG GLU LEU
SEQRES    6 A   295    LEU PHE ASN GLU VAL VAL ILE MET ARG ASP TYR GLN HIS
SEQRES    7 A   295    PHE ASN VAL VAL GLU MET TYR LYS SER TYR LEU VAL GLY
SEQRES    8 A   295    GLU GLU LEU TRP VAL LEU MET GLU PHE LEU GLN GLY GLY
SEQRES    9 A   295    ALA LEU THR ASP ILE VAL SER GLN VAL ARG LEU ASN GLU
SEQRES   10 A   295    GLU GLN ILE ALA THR VAL CYS GLU ALA VAL LEU GLN ALA
SEQRES   11 A   295    LEU ALA TYR LEU HIS ALA GLN GLY VAL ILE HIS ARG ASP
SEQRES   12 A   295    ILE LYS SER ASP SER ILE LEU LEU THR LEU ASP GLY ARG
SEQRES   13 A   295    VAL LYS LEU SER ASP PHE GLY PHE CYS ALA GLN ILE SER
SEQRES   14 A   295    LYS ASP VAL PRO LYS ARG LYS SEP LEU VAL GLY THR PRO
SEQRES   15 A   295    TYR TRP MET ALA PRO GLU VAL ILE SER ARG SER LEU TYR
SEQRES   16 A   295    ALA THR GLU VAL ASP ILE TRP SER LEU GLY ILE MET VAL
SEQRES   17 A   295    ILE GLU MET VAL ASP GLY GLU PRO PRO TYR PHE SER ASP
SEQRES   18 A   295    SER PRO VAL GLN ALA MET LYS ARG LEU ARG ASP SER PRO
SEQRES   19 A   295    PRO PRO LYS LEU LYS ASN SER HIS LYS VAL SER PRO VAL
SEQRES   20 A   295    LEU ARG ASP PHE LEU GLU ARG MET LEU VAL ARG ASP PRO
SEQRES   21 A   295    GLN GLU ARG ALA THR ALA GLN GLU LEU LEU ASP HIS PRO
SEQRES   22 A   295    PHE LEU LEU GLN THR GLY LEU PRO GLU CYS LEU VAL PRO
SEQRES   23 A   295    LEU ILE GLN LEU TYR ARG LYS GLU GLY
```

FIGURE 2

FIG. 3

CRYST1 59.242 66.718 97.213 90.00 90.00 90.00 P 21 21 21 4

	Atom Type	Residue	#	X	Y	Z	OCC	B	Atom
ATOM	1 N	SER A	1	4.255	69.582	-7.189	1.00	37.48	N
ATOM	2 CA	SER A	1	5.538	68.936	-6.810	1.00	37.14	C
ATOM	3 C	SER A	1	6.478	69.003	-8.019	1.00	34.33	C
ATOM	4 O	SER A	1	6.045	69.367	-9.121	1.00	34.04	O
ATOM	5 CB	SER A	1	5.282	67.476	-6.416	1.00	38.61	C
ATOM	6 OG	SER A	1	4.772	66.768	-7.542	1.00	42.89	O
ATOM	7 N	LEU A	2	7.741	68.627	-7.804	1.00	29.21	N
ATOM	8 CA	LEU A	2	8.735	68.581	-8.863	1.00	24.19	C
ATOM	9 C	LEU A	2	8.369	67.552	-9.936	1.00	23.79	C
ATOM	10 O	LEU A	2	7.887	66.435	-9.649	1.00	22.85	O
ATOM	11 CB	LEU A	2	10.121	68.278	-8.235	1.00	23.41	C
ATOM	12 CG	LEU A	2	10.709	69.380	-7.331	1.00	23.54	C
ATOM	13 CD1	LEU A	2	12.145	69.111	-6.891	1.00	25.23	C
ATOM	14 CD2	LEU A	2	10.630	70.780	-7.975	1.00	25.66	C
ATOM	15 N	THR A	3	8.628	67.866	-11.193	1.00	20.07	N
ATOM	16 CA	THR A	3	8.543	66.817	-12.192	1.00	18.28	C
ATOM	17 C	THR A	3	9.664	65.811	-11.944	1.00	16.21	C
ATOM	18 O	THR A	3	10.598	66.072	-11.146	1.00	17.46	O
ATOM	19 CB	THR A	3	8.714	67.404	-13.617	1.00	18.77	C
ATOM	20 OG1	THR A	3	10.037	67.979	-13.747	1.00	19.31	O
ATOM	21 CG2	THR A	3	7.741	68.587	-13.828	1.00	19.26	C
ATOM	22 N	HIS A	4	9.598	64.692	-12.677	1.00	15.92	N
ATOM	23 CA	HIS A	4	10.674	63.697	-12.624	1.00	15.47	C
ATOM	24 C	HIS A	4	12.040	64.304	-12.952	1.00	15.13	C
ATOM	25 O	HIS A	4	13.034	64.106	-12.229	1.00	14.28	O
ATOM	26 CB	HIS A	4	10.328	62.527	-13.538	1.00	16.70	C
ATOM	27 CG	HIS A	4	11.405	61.499	-13.646	1.00	18.74	C
ATOM	28 ND1	HIS A	4	11.867	60.786	-12.553	1.00	16.57	N
ATOM	29 CE1	HIS A	4	12.819	59.947	-12.952	1.00	18.77	C
ATOM	30 NE2	HIS A	4	13.016	60.122	-14.260	1.00	18.88	N
ATOM	31 CD2	HIS A	4	12.136	61.072	-14.713	1.00	16.88	C
ATOM	32 N	GLU A	5	12.096	65.079	-14.051	1.00	15.64	N
ATOM	33 CA	GLU A	5	13.341	65.723	-14.452	1.00	14.44	C
ATOM	34 C	GLU A	5	13.880	66.698	-13.398	1.00	13.99	C
ATOM	35 O	GLU A	5	15.072	66.706	-13.114	1.00	14.25	O
ATOM	36 CB	GLU A	5	13.183	66.393	-15.842	1.00	17.22	C
ATOM	37 CG	GLU A	5	12.961	65.370	-16.986	1.00	19.67	C
ATOM	38 N	GLN A	6	13.002	67.519	-12.837	1.00	14.17	N
ATOM	39 CA	GLN A	6	13.372	68.446	-11.773	1.00	12.69	C
ATOM	40 C	GLN A	6	13.851	67.682	-10.527	1.00	12.96	C
ATOM	41 O	GLN A	6	14.795	68.122	-9.890	1.00	13.85	O
ATOM	42 CB	GLN A	6	12.206	69.356	-11.355	1.00	14.71	C
ATOM	43 CG	GLN A	6	11.889	70.403	-12.402	1.00	14.71	C
ATOM	44 CD	GLN A	6	10.736	71.234	-11.957	1.00	18.09	C
ATOM	45 OE1	GLN A	6	9.704	70.691	-11.563	1.00	19.71	O
ATOM	46 NE2	GLN A	6	10.889	72.540	-11.996	1.00	18.73	N
ATOM	47 N	PHE A	7	13.149	66.594	-10.180	1.00	13.18	N
ATOM	48 CA	PHE A	7	13.576	65.856	-9.002	1.00	13.46	C
ATOM	49 C	PHE A	7	14.967	65.228	-9.179	1.00	12.12	C
ATOM	50 O	PHE A	7	15.800	65.298	-8.270	1.00	12.52	O
ATOM	51 CB	PHE A	7	12.525	64.820	-8.607	1.00	14.09	C
ATOM	52 CG	PHE A	7	12.837	64.178	-7.289	1.00	14.22	C
ATOM	53 CD1	PHE A	7	13.240	62.870	-7.258	1.00	18.17	C
ATOM	54 CE1	PHE A	7	13.556	62.242	-6.027	1.00	20.16	C
ATOM	55 CZ	PHE A	7	13.562	63.010	-4.858	1.00	18.29	C

FIGURE 4A

ATOM	56	CE2	PHE	A	7	13.169	64.352	-4.903	1.00	15.59	C
ATOM	57	CD2	PHE	A	7	12.829	64.928	-6.129	1.00	15.24	C
ATOM	58	N	LYS	A	8	15.242	64.632	-10.344	1.00	12.05	N
ATOM	59	CA	LYS	A	8	16.615	64.100	-10.599	1.00	13.93	C
ATOM	60	C	LYS	A	8	17.658	65.192	-10.445	1.00	12.47	C
ATOM	61	O	LYS	A	8	18.748	64.950	-9.871	1.00	13.87	O
ATOM	62	CB	LYS	A	8	16.779	63.491	-12.012	1.00	14.57	C
ATOM	63	CG	LYS	A	8	16.029	62.172	-12.163	1.00	14.30	C
ATOM	64	CD	LYS	A	8	16.429	61.472	-13.467	1.00	18.88	C
ATOM	65	CE	LYS	A	8	15.814	62.234	-14.607	1.00	20.22	C
ATOM	66	NZ	LYS	A	8	16.119	61.582	-15.919	1.00	20.03	N
ATOM	67	N	ALA	A	9	17.367	66.394	-10.951	1.00	14.03	N
ATOM	68	CA	ALA	A	9	18.346	67.485	-10.827	1.00	14.54	C
ATOM	69	C	ALA	A	9	18.595	67.897	-9.402	1.00	15.46	C
ATOM	70	O	ALA	A	9	19.741	68.188	-9.031	1.00	16.59	O
ATOM	71	CB	ALA	A	9	17.894	68.693	-11.706	1.00	15.19	C
ATOM	72	N	ALA	A	10	17.533	67.868	-8.585	1.00	14.46	N
ATOM	73	CA	ALA	A	10	17.643	68.204	-7.167	1.00	13.59	C
ATOM	74	C	ALA	A	10	18.505	67.108	-6.493	1.00	13.88	C
ATOM	75	O	ALA	A	10	19.410	67.403	-5.714	1.00	14.66	O
ATOM	76	CB	ALA	A	10	16.272	68.226	-6.529	1.00	16.88	C
ATOM	77	N	LEU	A	11	18.222	65.842	-6.794	1.00	13.13	N
ATOM	78	CA	LEU	A	11	19.023	64.740	-6.182	1.00	12.29	C
ATOM	79	C	LEU	A	11	20.467	64.798	-6.537	1.00	15.09	C
ATOM	80	O	LEU	A	11	21.349	64.449	-5.740	1.00	12.86	O
ATOM	81	CB	LEU	A	11	18.493	63.381	-6.622	1.00	14.59	C
ATOM	82	CG	LEU	A	11	17.316	62.889	-5.873	1.00	17.11	C
ATOM	83	CD1	LEU	A	11	16.871	61.586	-6.587	1.00	16.74	C
ATOM	84	CD2	LEU	A	11	17.706	62.644	-4.346	1.00	14.63	C
ATOM	85	N	ARG	A	12	20.743	65.234	-7.779	1.00	15.23	N
ATOM	86	CA	ARG	A	12	22.132	65.250	-8.197	1.00	19.00	C
ATOM	87	C	ARG	A	12	22.987	66.119	-7.326	1.00	19.99	C
ATOM	88	O	ARG	A	12	24.199	65.909	-7.222	1.00	23.19	O
ATOM	89	CB	ARG	A	12	22.245	65.740	-9.640	1.00	20.72	C
ATOM	90	CG	BARG	A	12	21.680	64.776	-10.661	0.25	18.88	C
ATOM	91	CG	AARG	A	12	22.271	64.657	-10.588	0.75	21.37	C
ATOM	92	CD	BARG	A	12	22.457	64.703	-12.006	0.25	20.36	C
ATOM	93	CD	AARG	A	12	22.567	65.121	-12.042	0.75	20.08	C
ATOM	94	NE	BARG	A	12	22.285	63.396	-12.639	0.25	20.74	N
ATOM	95	NE	AARG	A	12	21.810	64.220	-12.856	0.75	16.51	N
ATOM	96	CZ	BARG	A	12	23.195	62.422	-12.664	0.25	19.97	C
ATOM	97	CZ	AARG	A	12	20.687	64.526	-13.470	0.75	14.33	C
ATOM	98	NH1	BARG	A	12	24.396	62.594	-12.129	0.25	20.48	N
ATOM	99	NH1	AARG	A	12	20.244	65.775	-13.471	0.75	14.60	N
ATOM	100	NH2	BARG	A	12	22.903	61.277	-13.256	0.25	20.12	N
ATOM	101	NH2	AARG	A	12	20.037	63.567	-14.086	0.75	14.64	N
ATOM	102	N	MET	A	13	22.391	67.107	-6.705	1.00	21.69	N
ATOM	103	CA	MET	A	13	23.132	67.991	-5.819	1.00	25.09	C
ATOM	104	C	MET	A	13	23.521	67.344	-4.476	1.00	23.34	C
ATOM	105	O	MET	A	13	24.463	67.797	-3.844	1.00	24.70	O
ATOM	106	CB	MET	A	13	22.332	69.270	-5.545	1.00	27.66	C
ATOM	107	CG	MET	A	13	21.864	70.008	-6.805	1.00	35.01	C
ATOM	108	SD	MET	A	13	23.223	70.327	-7.952	1.00	49.17	S
ATOM	109	CE	MET	A	13	24.051	71.787	-7.093	1.00	49.02	C
ATOM	110	N	VAL	A	14	22.823	66.277	-4.068	1.00	17.63	N
ATOM	111	CA	VAL	A	14	22.997	65.734	-2.731	1.00	17.18	C
ATOM	112	C	VAL	A	14	23.452	64.289	-2.628	1.00	16.20	C
ATOM	113	O	VAL	A	14	23.824	63.812	-1.533	1.00	17.02	O
ATOM	114	CB	VAL	A	14	21.669	65.947	-1.894	1.00	17.40	C
ATOM	115	CG1	VAL	A	14	21.251	67.444	-1.891	1.00	20.61	C

FIGURE 4B

ATOM	116	CG2	VAL	A	14	20.521	65.056	-2.439	1.00	18.92	C
ATOM	117	N	VAL	A	15	23.375	63.540	-3.743	1.00	14.22	N
ATOM	118	CA	VAL	A	15	23.815	62.157	-3.643	1.00	13.93	C
ATOM	119	C	VAL	A	15	25.342	62.069	-3.693	1.00	13.29	C
ATOM	120	O	VAL	A	15	26.038	63.039	-4.027	1.00	14.68	O
ATOM	121	CB	VAL	A	15	23.249	61.270	-4.760	1.00	14.80	C
ATOM	122	CG1	VAL	A	15	21.744	61.193	-4.633	1.00	13.87	C
ATOM	123	CG2	VAL	A	15	23.685	61.804	-6.155	1.00	14.96	C
ATOM	124	N	ASP	A	16	25.873	60.887	-3.360	1.00	12.93	N
ATOM	125	CA	ASP	A	16	27.292	60.642	-3.567	1.00	15.58	C
ATOM	126	C	ASP	A	16	27.624	60.619	-5.051	1.00	16.44	C
ATOM	127	O	ASP	A	16	26.792	60.259	-5.888	1.00	17.39	O
ATOM	128	CB	ASP	A	16	27.718	59.325	-2.903	1.00	16.08	C
ATOM	129	CG	ASP	A	16	27.580	59.399	-1.391	1.00	17.67	C
ATOM	130	OD1	ASP	A	16	28.522	59.885	-0.715	1.00	21.90	O
ATOM	131	OD2	ASP	A	16	26.529	59.046	-0.769	1.00	18.66	O
ATOM	132	N	GLN	A	17	28.872	60.996	-5.330	1.00	21.30	N
ATOM	133	CA	GLN	A	17	29.381	60.965	-6.692	1.00	25.06	C
ATOM	134	C	GLN	A	17	29.886	59.565	-6.964	1.00	25.21	C
ATOM	135	O	GLN	A	17	30.388	58.864	-6.078	1.00	26.76	O
ATOM	136	CB	GLN	A	17	30.555	61.968	-6.858	1.00	27.80	C
ATOM	137	CG	GLN	A	17	30.126	63.437	-6.697	1.00	34.95	C
ATOM	138	CD	GLN	A	17	28.856	63.768	-7.461	1.00	40.64	C
ATOM	139	OE1	GLN	A	17	28.890	63.948	-8.687	1.00	45.27	O
ATOM	140	NE2	GLN	A	17	27.734	63.841	-6.754	1.00	44.64	N
ATOM	141	N	GLY	A	18	29.808	59.167	-8.207	1.00	26.04	N
ATOM	142	CA	GLY	A	18	30.404	57.892	-8.558	1.00	23.61	C
ATOM	143	C	GLY	A	18	29.253	57.041	-9.058	1.00	22.95	C
ATOM	144	O	GLY	A	18	28.079	57.389	-8.927	1.00	23.97	O
ATOM	145	N	ASP	A	19	29.605	55.928	-9.696	1.00	19.46	N
ATOM	146	CA	ASP	A	19	28.566	55.126	-10.303	1.00	15.13	C
ATOM	147	C	ASP	A	19	28.675	53.767	-9.671	1.00	13.30	C
ATOM	148	O	ASP	A	19	29.687	53.043	-9.834	1.00	14.96	O
ATOM	149	CB	ASP	A	19	28.801	55.078	-11.815	1.00	15.80	C
ATOM	150	CG	ASP	A	19	27.693	54.323	-12.543	1.00	14.82	C
ATOM	151	OD1	ASP	A	19	27.397	54.694	-13.708	1.00	22.17	O
ATOM	152	OD2	ASP	A	19	27.014	53.415	-12.012	1.00	13.19	O
ATOM	153	N	PRO	A	20	27.676	53.345	-8.895	1.00	10.70	N
ATOM	154	CA	PRO	A	20	27.815	52.111	-8.148	1.00	11.44	C
ATOM	155	C	PRO	A	20	27.794	50.857	-9.034	1.00	11.73	C
ATOM	156	O	PRO	A	20	28.133	49.785	-8.520	1.00	13.50	O
ATOM	157	CB	PRO	A	20	26.577	52.089	-7.236	1.00	11.63	C
ATOM	158	CG	PRO	A	20	25.536	52.923	-8.012	1.00	11.68	C
ATOM	159	CD	PRO	A	20	26.354	53.992	-8.704	1.00	13.09	C
ATOM	160	N	ARG	A	21	27.487	51.023	-10.307	1.00	10.30	N
ATOM	161	CA	ARG	A	21	27.540	49.878	-11.218	1.00	9.94	C
ATOM	162	C	ARG	A	21	28.981	49.463	-11.431	1.00	12.33	C
ATOM	163	O	ARG	A	21	29.214	48.347	-11.894	1.00	11.88	O
ATOM	164	CB	ARG	A	21	26.860	50.230	-12.541	1.00	9.53	C
ATOM	165	CG	ARG	A	21	25.320	50.246	-12.351	1.00	12.08	C
ATOM	166	CD	ARG	A	21	24.619	50.877	-13.551	1.00	13.29	C
ATOM	167	NE	ARG	A	21	24.988	52.285	-13.741	1.00	11.04	N
ATOM	168	CZ	ARG	A	21	24.332	53.100	-14.566	1.00	14.55	C
ATOM	169	NH1	ARG	A	21	23.367	52.624	-15.329	1.00	15.02	N
ATOM	170	NH2	ARG	A	21	24.646	54.393	-14.647	1.00	17.49	N
ATOM	171	N	LEU	A	22	29.934	50.320	-11.100	1.00	12.18	N
ATOM	172	CA	LEU	A	22	31.345	49.927	-11.105	1.00	14.51	C
ATOM	173	C	LEU	A	22	31.857	49.483	-9.729	1.00	15.14	C
ATOM	174	O	LEU	A	22	32.918	48.883	-9.632	1.00	17.84	O
ATOM	175	CB	LEU	A	22	32.203	51.107	-11.619	1.00	14.34	C

FIGURE 4C

ATOM	176	CG	LEU	A	22	32.122	51.159	-13.157	1.00	17.03	C
ATOM	177	CD1	LEU	A	22	30.826	51.853	-13.602	1.00	19.85	C
ATOM	178	CD2	LEU	A	22	33.357	51.826	-13.741	1.00	25.07	C
ATOM	179	N	LEU	A	23	31.156	49.866	-8.653	1.00	13.13	N
ATOM	180	CA	LEU	A	23	31.658	49.731	-7.300	1.00	11.50	C
ATOM	181	C	LEU	A	23	31.136	48.525	-6.502	1.00	12.61	C
ATOM	182	O	LEU	A	23	31.640	48.214	-5.426	1.00	15.30	O
ATOM	183	CB	LEU	A	23	31.254	50.973	-6.494	1.00	11.09	C
ATOM	184	CG	LEU	A	23	31.718	52.310	-7.093	1.00	14.53	C
ATOM	185	CD1	LEU	A	23	31.083	53.439	-6.284	1.00	17.73	C
ATOM	186	CD2	LEU	A	23	33.278	52.458	-7.056	1.00	19.49	C
ATOM	187	N	LEU	A	24	30.117	47.860	-7.024	1.00	10.67	N
ATOM	188	CA	LEU	A	24	29.472	46.769	-6.315	1.00	9.69	C
ATOM	189	C	LEU	A	24	29.522	45.511	-7.175	1.00	9.07	C
ATOM	190	O	LEU	A	24	29.640	45.575	-8.418	1.00	12.00	O
ATOM	191	CB	LEU	A	24	27.982	47.126	-6.085	1.00	10.47	C
ATOM	192	CG	LEU	A	24	27.719	48.442	-5.317	1.00	11.73	C
ATOM	193	CD1	LEU	A	24	26.212	48.632	-5.202	1.00	12.94	C
ATOM	194	CD2	LEU	A	24	28.362	48.259	-3.906	1.00	15.84	C
ATOM	195	N	ASP	A	25	29.384	44.366	-6.533	1.00	9.18	N
ATOM	196	CA	ASP	A	25	29.209	43.100	-7.268	1.00	11.54	C
ATOM	197	C	ASP	A	25	28.442	42.104	-6.438	1.00	12.11	C
ATOM	198	O	ASP	A	25	27.953	42.469	-5.350	1.00	12.78	O
ATOM	199	CB	ASP	A	25	30.589	42.584	-7.726	1.00	12.54	C
ATOM	200	CG	ASP	A	25	31.498	42.280	-6.571	1.00	19.17	C
ATOM	201	OD1	ASP	A	25	32.601	42.851	-6.523	1.00	20.54	O
ATOM	202	OD2	ASP	A	25	31.177	41.478	-5.657	1.00	22.03	O
ATOM	203	N	SER	A	26	28.310	40.856	-6.927	1.00	12.85	N
ATOM	204	CA	SER	A	26	27.654	39.786	-6.172	1.00	15.16	C
ATOM	205	C	SER	A	26	26.224	40.125	-5.787	1.00	14.02	C
ATOM	206	O	SER	A	26	25.815	39.942	-4.637	1.00	15.44	O
ATOM	207	CB	SER	A	26	28.468	39.392	-4.906	1.00	15.47	C
ATOM	208	OG	SER	A	26	29.796	39.109	-5.306	1.00	19.79	O
ATOM	209	N	TYR	A	27	25.462	40.634	-6.733	1.00	12.48	N
ATOM	210	CA	TYR	A	27	24.095	41.020	-6.456	1.00	11.57	C
ATOM	211	C	TYR	A	27	23.207	39.841	-6.327	1.00	15.74	C
ATOM	212	O	TYR	A	27	23.236	38.948	-7.181	1.00	15.92	O
ATOM	213	CB	TYR	A	27	23.532	41.867	-7.616	1.00	12.55	C
ATOM	214	CG	TYR	A	27	24.183	43.196	-7.881	1.00	12.17	C
ATOM	215	CD1	TYR	A	27	23.648	44.383	-7.338	1.00	11.29	C
ATOM	216	CE1	TYR	A	27	24.229	45.662	-7.606	1.00	13.77	C
ATOM	217	CZ	TYR	A	27	25.389	45.709	-8.427	1.00	11.76	C
ATOM	218	OH	TYR	A	27	25.907	46.910	-8.753	1.00	12.42	O
ATOM	219	CE2	TYR	A	27	25.934	44.526	-8.979	1.00	10.35	C
ATOM	220	CD2	TYR	A	27	25.329	43.295	-8.699	1.00	12.94	C
ATOM	221	N	VAL	A	28	22.341	39.896	-5.322	1.00	14.82	N
ATOM	222	CA	VAL	A	28	21.270	38.913	-5.169	1.00	17.64	C
ATOM	223	C	VAL	A	28	19.981	39.626	-4.821	1.00	15.47	C
ATOM	224	O	VAL	A	28	19.928	40.300	-3.818	1.00	16.40	O
ATOM	225	CB	VAL	A	28	21.619	37.928	-4.030	1.00	17.98	C
ATOM	226	CG1	VAL	A	28	20.422	36.952	-3.756	1.00	21.29	C
ATOM	227	CG2	VAL	A	28	22.971	37.155	-4.301	1.00	21.24	C
ATOM	228	N	LYS	A	29	18.918	39.479	-5.643	1.00	17.26	N
ATOM	229	CA	LYS	A	29	17.623	40.098	-5.360	1.00	19.09	C
ATOM	230	C	LYS	A	29	16.955	39.465	-4.150	1.00	21.14	C
ATOM	231	O	LYS	A	29	16.820	38.221	-4.097	1.00	22.83	O
ATOM	232	CB	LYS	A	29	16.705	40.042	-6.581	1.00	22.10	C
ATOM	233	CG	LYS	A	29	15.420	40.856	-6.369	1.00	23.81	C
ATOM	234	CD	LYS	A	29	14.628	40.912	-7.667	1.00	29.03	C
ATOM	235	CE	LYS	A	29	13.166	40.797	-7.314	1.00	32.57	C

FIGURE 4D

ATOM	236	NZ	LYS A	29	12.346	40.770	-8.562	1.00	35.07	N
ATOM	237	N	ILE A	30	16.578	40.280	-3.182	1.00	20.16	N
ATOM	238	CA	ILE A	30	15.970	39.734	-1.955	1.00	22.42	C
ATOM	239	C	ILE A	30	14.610	40.324	-1.607	1.00	24.96	C
ATOM	240	O	ILE A	30	13.981	39.883	-0.644	1.00	25.98	O
ATOM	241	CB	ILE A	30	16.855	39.876	-0.720	1.00	21.78	C
ATOM	242	CG1	ILE A	30	17.176	41.348	-0.421	1.00	21.08	C
ATOM	243	CD1	ILE A	30	17.751	41.503	0.977	1.00	23.90	C
ATOM	244	CG2	ILE A	30	18.109	39.003	-0.828	1.00	21.19	C
ATOM	245	N	GLY A	31	14.180	41.328	-2.355	1.00	24.54	N
ATOM	246	CA	GLY A	31	12.974	42.086	-2.027	1.00	27.36	C
ATOM	247	C	GLY A	31	12.434	42.685	-3.315	1.00	27.39	C
ATOM	248	O	GLY A	31	13.191	43.015	-4.234	1.00	24.68	O
ATOM	249	N	GLU A	32	11.111	42.777	-3.412	1.00	29.35	N
ATOM	250	CA	GLU A	32	10.500	43.477	-4.535	1.00	34.01	C
ATOM	251	C	GLU A	32	9.260	44.239	-4.029	1.00	34.48	C
ATOM	252	O	GLU A	32	8.537	43.811	-3.088	1.00	34.78	O
ATOM	253	CB	GLU A	32	10.181	42.568	-5.741	1.00	35.60	C
ATOM	254	CG	GLU A	32	10.174	43.334	-7.075	1.00	41.71	C
ATOM	255	CD	GLU A	32	9.729	42.528	-8.305	1.00	46.73	C
ATOM	256	OE1	GLU A	32	8.551	42.098	-8.370	1.00	50.73	O
ATOM	257	OE2	GLU A	32	10.544	42.349	-9.249	1.00	48.84	O
ATOM	258	N	GLY A	33	9.044	45.390	-4.641	1.00	32.68	N
ATOM	259	CA	GLY A	33	8.041	46.324	-4.162	1.00	32.36	C
ATOM	260	C	GLY A	33	7.418	46.911	-5.403	1.00	29.65	C
ATOM	261	O	GLY A	33	7.779	46.538	-6.546	1.00	29.02	O
ATOM	262	N	SER A	34	6.441	47.790	-5.196	1.00	29.93	N
ATOM	263	CA	SER A	34	5.792	48.393	-6.351	1.00	28.24	C
ATOM	264	C	SER A	34	6.677	49.426	-7.023	1.00	27.38	C
ATOM	265	O	SER A	34	6.457	49.780	-8.167	1.00	27.56	O
ATOM	266	CB	SER A	34	4.424	48.989	-5.984	1.00	27.18	C
ATOM	267	OG	SER A	34	4.530	50.090	-5.086	1.00	29.14	O
ATOM	268	N	THR A	35	7.687	49.906	-6.314	1.00	25.69	N
ATOM	269	CA	THR A	35	8.459	51.023	-6.848	1.00	26.40	C
ATOM	270	C	THR A	35	9.932	50.642	-7.060	1.00	26.80	C
ATOM	271	O	THR A	35	10.738	51.492	-7.429	1.00	27.06	O
ATOM	272	CB	THR A	35	8.350	52.302	-5.959	1.00	27.03	C
ATOM	273	OG1	THR A	35	8.741	51.999	-4.601	1.00	32.51	O
ATOM	274	CG2	THR A	35	6.926	52.800	-5.856	1.00	25.64	C
ATOM	275	N	GLY A	36	10.279	49.377	-6.812	1.00	25.76	N
ATOM	276	CA	GLY A	36	11.662	48.950	-7.013	1.00	24.96	C
ATOM	277	C	GLY A	36	12.025	47.650	-6.347	1.00	26.10	C
ATOM	278	O	GLY A	36	11.161	46.847	-5.980	1.00	24.93	O
ATOM	279	N	ILE A	37	13.323	47.389	-6.248	1.00	21.07	N
ATOM	280	CA	ILE A	37	13.763	46.137	-5.660	1.00	20.68	C
ATOM	281	C	ILE A	37	14.810	46.385	-4.580	1.00	20.77	C
ATOM	282	O	ILE A	37	15.290	47.514	-4.395	1.00	17.69	O
ATOM	283	CB	ILE A	37	14.304	45.202	-6.733	1.00	21.29	C
ATOM	284	CG1	ILE A	37	15.590	45.787	-7.358	1.00	21.98	C
ATOM	285	CD1	ILE A	37	16.331	44.800	-8.270	1.00	24.25	C
ATOM	286	CG2	ILE A	37	13.274	44.943	-7.852	1.00	24.04	C
ATOM	287	N	VAL A	38	15.133	45.331	-3.822	1.00	16.94	N
ATOM	288	CA	VAL A	38	16.261	45.380	-2.925	1.00	17.77	C
ATOM	289	C	VAL A	38	17.176	44.236	-3.312	1.00	17.91	C
ATOM	290	O	VAL A	38	16.701	43.121	-3.503	1.00	16.89	O
ATOM	291	CB	VAL A	38	15.849	45.213	-1.464	1.00	20.06	C
ATOM	292	CG1	VAL A	38	17.068	45.278	-0.574	1.00	19.53	C
ATOM	293	CG2	VAL A	38	14.878	46.355	-1.058	1.00	22.63	C
ATOM	294	N	CYS A	39	18.466	44.535	-3.504	1.00	15.90	N
ATOM	295	CA	CYS A	39	19.462	43.492	-3.802	1.00	15.23	C

FIGURE 4E

ATOM	296	C	CYS	A	39	20.487	43.558	-2.718	1.00	15.09	C
ATOM	297	O	CYS	A	39	20.916	44.644	-2.307	1.00	18.31	O
ATOM	298	CB	CYS	A	39	20.206	43.780	-5.085	1.00	17.71	C
ATOM	299	SG	CYS	A	39	19.248	43.345	-6.531	1.00	29.98	S
ATOM	300	N	LEU	A	40	20.935	42.404	-2.280	1.00	13.43	N
ATOM	301	CA	LEU	A	40	22.176	42.366	-1.504	1.00	12.61	C
ATOM	302	C	LEU	A	40	23.316	42.478	-2.461	1.00	13.56	C
ATOM	303	O	LEU	A	40	23.229	41.998	-3.582	1.00	13.95	O
ATOM	304	CB B	LEU	A	40	22.205	41.014	-0.818	0.35	13.47	C
ATOM	305	CB A	LEU	A	40	22.313	41.061	-0.726	0.65	13.78	C
ATOM	306	CG B	LEU	A	40	23.084	40.728	0.369	0.35	13.46	C
ATOM	307	CG A	LEU	A	40	21.295	40.911	0.371	0.65	14.42	C
ATOM	308	CD1 B	LEU	A	40	22.868	41.756	1.476	0.35	12.14	C
ATOM	309	CD1 A	LEU	A	40	21.485	39.526	1.072	0.65	16.48	C
ATOM	310	CD2 B	LEU	A	40	22.690	39.340	0.836	0.35	14.25	C
ATOM	311	CD2 A	LEU	A	40	21.438	42.036	1.398	0.65	12.51	C
ATOM	312	N	ALA	A	41	24.402	43.093	-2.059	1.00	11.04	N
ATOM	313	CA	ALA	A	41	25.588	43.173	-2.932	1.00	9.78	C
ATOM	314	C	ALA	A	41	26.776	43.339	-2.028	1.00	11.45	C
ATOM	315	O	ALA	A	41	26.624	43.526	-0.806	1.00	12.40	O
ATOM	316	CB	ALA	A	41	25.445	44.398	-3.909	1.00	11.45	C
ATOM	317	N	ARG	A	42	27.957	43.287	-2.631	1.00	10.09	N
ATOM	318	CA	ARG	A	42	29.214	43.485	-1.901	1.00	12.07	C
ATOM	319	C	ARG	A	42	29.923	44.700	-2.438	1.00	12.90	C
ATOM	320	O	ARG	A	42	29.991	44.899	-3.658	1.00	13.27	O
ATOM	321	CB	ARG	A	42	30.129	42.285	-2.126	1.00	13.30	C
ATOM	322	CG	ARG	A	42	29.677	40.964	-1.510	1.00	17.03	C
ATOM	323	CD	ARG	A	42	30.194	40.836	-0.116	1.00	18.50	C
ATOM	324	NE	ARG	A	42	29.707	39.625	0.515	1.00	20.90	N
ATOM	325	CZ	ARG	A	42	30.001	39.313	1.774	1.00	21.98	C
ATOM	326	NH1	ARG	A	42	30.809	40.101	2.484	1.00	20.65	N
ATOM	327	NH2	ARG	A	42	29.485	38.235	2.323	1.00	24.90	N
ATOM	328	N	GLU	A	43	30.447	45.538	-1.546	1.00	13.14	N
ATOM	329	CA	GLU	A	43	31.287	46.651	-1.947	1.00	16.07	C
ATOM	330	C	GLU	A	43	32.680	46.158	-2.283	1.00	17.93	C
ATOM	331	O	GLU	A	43	33.280	45.318	-1.598	1.00	17.37	O
ATOM	332	CB	GLU	A	43	31.356	47.712	-0.788	1.00	17.80	C
ATOM	333	CG	GLU	A	43	30.062	48.500	-0.603	1.00	24.14	C
ATOM	334	CD	GLU	A	43	30.170	49.753	0.323	1.00	36.79	C
ATOM	335	OE1	GLU	A	43	29.840	50.931	-0.087	1.00	40.88	O
ATOM	336	OE2	GLU	A	43	30.548	49.583	1.488	1.00	37.74	O
ATOM	337	N	LYS	A	44	33.228	46.635	-3.401	1.00	18.53	N
ATOM	338	CA	LYS	A	44	34.595	46.237	-3.710	1.00	20.85	C
ATOM	339	C	LYS	A	44	35.580	46.850	-2.697	1.00	22.22	C
ATOM	340	O	LYS	A	44	35.313	47.903	-2.153	1.00	24.01	O
ATOM	341	CB	LYS	A	44	34.927	46.681	-5.150	1.00	20.91	C
ATOM	342	CG	LYS	A	44	34.118	45.798	-6.134	1.00	21.24	C
ATOM	343	CD	LYS	A	44	34.500	46.034	-7.588	1.00	23.03	C
ATOM	344	CE	LYS	A	44	33.451	45.426	-8.513	1.00	21.79	C
ATOM	345	NZ	LYS	A	44	33.802	43.999	-8.787	1.00	22.44	N
ATOM	346	N	HIS	A	45	36.705	46.175	-2.448	1.00	24.80	N
ATOM	347	CA	HIS	A	45	37.816	46.704	-1.561	1.00	28.55	C
ATOM	348	C	HIS	A	45	37.590	46.436	-0.072	1.00	27.31	C
ATOM	349	O	HIS	A	45	38.460	45.828	0.601	1.00	30.94	O
ATOM	350	CB	HIS	A	45	38.113	48.222	-1.732	1.00	31.19	C
ATOM	351	CG	HIS	A	45	38.483	48.624	-3.133	1.00	37.69	C
ATOM	352	ND1	HIS	A	45	39.598	48.134	-3.782	1.00	42.26	N
ATOM	353	CE1	HIS	A	45	39.656	48.649	-5.000	1.00	43.74	C
ATOM	354	NE2	HIS	A	45	38.628	49.466	-5.160	1.00	41.58	N
ATOM	355	CD2	HIS	A	45	37.885	49.477	-4.004	1.00	39.95	C

FIGURE 4F

ATOM	356	N	SER	A	46	36.432	46.876	0.437	1.00	26.00	N
ATOM	357	CA	SER	A	46	36.019	46.555	1.812	1.00	22.54	C
ATOM	358	C	SER	A	46	35.367	45.198	1.963	1.00	20.76	C
ATOM	359	O	SER	A	46	35.445	44.571	3.036	1.00	17.78	O
ATOM	360	CB	SER	A	46	35.066	47.606	2.338	1.00	22.04	C
ATOM	361	OG	SER	A	46	33.764	47.416	1.814	1.00	24.93	O
ATOM	362	N	GLY	A	47	34.686	44.737	0.916	1.00	17.17	N
ATOM	363	CA	GLY	A	47	34.033	43.468	1.021	1.00	16.12	C
ATOM	364	C	GLY	A	47	32.692	43.563	1.705	1.00	15.11	C
ATOM	365	O	GLY	A	47	32.043	42.570	1.848	1.00	16.73	O
ATOM	366	N	ARG	A	48	32.308	44.755	2.122	1.00	15.32	N
ATOM	367	CA	ARG	A	48	31.146	44.851	2.972	1.00	16.46	C
ATOM	368	C	ARG	A	48	29.857	44.444	2.220	1.00	16.46	C
ATOM	369	O	ARG	A	48	29.607	44.858	1.097	1.00	13.90	O
ATOM	370	CB	ARG	A	48	31.066	46.292	3.466	1.00	18.28	C
ATOM	371	CG	ARG	A	48	29.954	46.548	4.427	1.00	21.92	C
ATOM	372	CD	ARG	A	48	30.146	47.877	5.198	1.00	24.00	C
ATOM	373	NE	ARG	A	48	30.185	49.028	4.317	1.00	23.46	N
ATOM	374	CZ	ARG	A	48	30.420	50.277	4.711	1.00	26.94	C
ATOM	375	NH1	ARG	A	48	30.427	51.247	3.814	1.00	27.09	N
ATOM	376	NH2	ARG	A	48	30.665	50.544	6.000	1.00	23.89	N
ATOM	377	N	GLN	A	49	29.026	43.690	2.892	1.00	14.37	N
ATOM	378	CA	GLN	A	49	27.714	43.347	2.371	1.00	16.62	C
ATOM	379	C	GLN	A	49	26.784	44.519	2.622	1.00	15.48	C
ATOM	380	O	GLN	A	49	26.757	45.084	3.735	1.00	17.38	O
ATOM	381	CB	GLN	A	49	27.255	42.044	3.047	1.00	19.35	C
ATOM	382	CG	GLN	A	49	25.973	41.508	2.537	1.00	25.61	C
ATOM	383	CD	GLN	A	49	25.731	40.074	3.025	1.00	29.90	C
ATOM	384	OE1	GLN	A	49	25.694	39.820	4.227	1.00	35.77	O
ATOM	385	NE2	GLN	A	49	25.654	39.152	2.104	1.00	32.39	N
ATOM	386	N	VAL	A	50	26.009	44.911	1.605	1.00	12.13	N
ATOM	387	CA	VAL	A	50	25.077	46.052	1.738	1.00	12.23	C
ATOM	388	C	VAL	A	50	23.753	45.665	1.139	1.00	12.53	C
ATOM	389	O	VAL	A	50	23.675	44.827	0.240	1.00	13.60	O
ATOM	390	CB	VAL	A	50	25.586	47.339	0.996	1.00	11.34	C
ATOM	391	CG1	VAL	A	50	26.863	47.886	1.664	1.00	13.54	C
ATOM	392	CG2	VAL	A	50	25.814	47.101	-0.481	1.00	11.75	C
ATOM	393	N	ALA	A	51	22.683	46.261	1.655	1.00	11.02	N
ATOM	394	CA	ALA	A	51	21.371	46.115	1.049	1.00	12.40	C
ATOM	395	C	ALA	A	51	21.096	47.299	0.189	1.00	12.22	C
ATOM	396	O	ALA	A	51	21.021	48.423	0.691	1.00	17.98	O
ATOM	397	CB	ALA	A	51	20.298	46.028	2.152	1.00	14.02	C
ATOM	398	N	VAL	A	52	20.943	47.067	-1.105	1.00	11.18	N
ATOM	399	CA	VAL	A	52	20.844	48.199	-2.021	1.00	13.17	C
ATOM	400	C	VAL	A	52	19.362	48.316	-2.351	1.00	13.63	C
ATOM	401	O	VAL	A	52	18.811	47.448	-3.030	1.00	14.47	O
ATOM	402	CB	VAL	A	52	21.629	47.962	-3.335	1.00	12.75	C
ATOM	403	CG1	VAL	A	52	21.538	49.235	-4.289	1.00	11.81	C
ATOM	404	CG2	VAL	A	52	23.068	47.576	-3.032	1.00	12.68	C
ATOM	405	N	LYS	A	53	18.731	49.391	-1.895	1.00	14.05	N
ATOM	406	CA	LYS	A	53	17.371	49.681	-2.341	1.00	15.39	C
ATOM	407	C	LYS	A	53	17.473	50.432	-3.668	1.00	13.89	C
ATOM	408	O	LYS	A	53	18.092	51.522	-3.724	1.00	14.24	O
ATOM	409	CB	LYS	A	53	16.686	50.550	-1.319	1.00	17.12	C
ATOM	410	CG	LYS	A	53	16.663	49.947	0.113	1.00	21.94	C
ATOM	411	CD	LYS	A	53	16.074	50.989	1.134	1.00	26.70	C
ATOM	412	N	MET	A	54	16.878	49.866	-4.712	1.00	13.18	N
ATOM	413	CA	MET	A	54	16.929	50.430	-6.068	1.00	12.40	C
ATOM	414	C	MET	A	54	15.532	50.906	-6.383	1.00	15.36	C
ATOM	415	O	MET	A	54	14.665	50.073	-6.652	1.00	16.74	O

FIGURE 4G

ATOM	416	CB	MET	A	54	17.342	49.389	-7.063	1.00	13.00	C
ATOM	417	CG	MET	A	54	18.740	48.812	-6.710	1.00	13.28	C
ATOM	418	SD	MET	A	54	19.114	47.326	-7.684	1.00	19.83	S
ATOM	419	CE	MET	A	54	20.954	47.018	-7.327	1.00	15.36	C
ATOM	420	N	MET	A	55	15.315	52.188	-6.258	1.00	15.00	N
ATOM	421	CA	MET	A	55	13.969	52.799	-6.438	1.00	16.85	C
ATOM	422	C	MET	A	55	13.754	53.445	-7.776	1.00	14.40	C
ATOM	423	O	MET	A	55	14.524	54.299	-8.181	1.00	14.60	O
ATOM	424	CB	BMET	A	55	13.742	53.884	-5.371	0.35	15.51	C
ATOM	425	CB	AMET	A	55	13.667	53.823	-5.361	0.65	15.96	C
ATOM	426	CG	BMET	A	55	14.554	53.706	-4.098	0.35	18.74	C
ATOM	427	CG	AMET	A	55	13.248	53.182	-4.075	0.65	24.80	C
ATOM	428	SD	BMET	A	55	13.768	52.512	-3.033	0.35	21.92	S
ATOM	429	SD	AMET	A	55	13.737	54.316	-2.846	0.65	27.43	S
ATOM	430	CE	BMET	A	55	12.233	53.426	-2.562	0.35	21.78	C
ATOM	431	CE	AMET	A	55	15.399	53.802	-2.732	0.65	23.91	C
ATOM	432	N	ASP	A	56	12.672	53.111	-8.457	1.00	15.55	N
ATOM	433	CA	ASP	A	56	12.432	53.711	-9.753	1.00	15.83	C
ATOM	434	C	ASP	A	56	11.720	55.035	-9.469	1.00	14.23	C
ATOM	435	O	ASP	A	56	10.616	55.046	-8.944	1.00	16.20	O
ATOM	436	CB	ASP	A	56	11.524	52.824	-10.603	1.00	18.00	C
ATOM	437	CG	ASP	A	56	11.155	53.459	-11.954	1.00	23.66	C
ATOM	438	OD1	ASP	A	56	11.356	54.676	-12.227	1.00	24.76	O
ATOM	439	OD2	ASP	A	56	10.584	52.770	-12.826	1.00	31.97	O
ATOM	440	N	LEU	A	57	12.387	56.141	-9.740	1.00	14.36	N
ATOM	441	CA	LEU	A	57	11.876	57.452	-9.345	1.00	13.11	C
ATOM	442	C	LEU	A	57	10.643	57.844	-10.122	1.00	16.49	C
ATOM	443	O	LEU	A	57	9.887	58.714	-9.693	1.00	16.35	O
ATOM	444	CB	LEU	A	57	12.968	58.556	-9.496	1.00	13.23	C
ATOM	445	CG	LEU	A	57	14.131	58.333	-8.491	1.00	14.74	C
ATOM	446	CD1	LEU	A	57	15.286	59.249	-8.835	1.00	16.01	C
ATOM	447	CD2	LEU	A	57	13.619	58.607	-7.055	1.00	16.26	C
ATOM	448	N	ARG	A	58	10.423	57.206	-11.258	1.00	16.47	N
ATOM	449	CA	ARG	A	58	9.200	57.506	-12.031	1.00	20.66	C
ATOM	450	C	ARG	A	58	7.983	56.927	-11.383	1.00	21.68	C
ATOM	451	O	ARG	A	58	6.873	57.382	-11.637	1.00	27.31	O
ATOM	452	CB	ARG	A	58	9.342	56.984	-13.456	1.00	22.28	C
ATOM	453	CG	ARG	A	58	10.282	57.837	-14.281	1.00	25.01	C
ATOM	454	CD	ARG	A	58	10.810	57.178	-15.512	1.00	30.40	C
ATOM	455	NE	ARG	A	58	11.205	55.808	-15.233	1.00	33.95	N
ATOM	456	CZ	ARG	A	58	11.740	54.977	-16.114	1.00	39.54	C
ATOM	457	NH1	ARG	A	58	11.993	55.372	-17.365	1.00	42.52	N
ATOM	458	NH2	ARG	A	58	12.042	53.744	-15.732	1.00	41.70	N
ATOM	459	N	LYS	A	59	8.170	55.919	-10.538	1.00	19.43	N
ATOM	460	CA	LYS	A	59	7.068	55.283	-9.841	1.00	20.52	C
ATOM	461	C	LYS	A	59	6.932	55.781	-8.404	1.00	21.10	C
ATOM	462	O	LYS	A	59	5.851	55.747	-7.810	1.00	21.07	O
ATOM	463	CB	LYS	A	59	7.252	53.764	-9.867	1.00	20.25	C
ATOM	464	CG	LYS	A	59	7.221	53.194	-11.289	1.00	24.36	C
ATOM	465	CD	LYS	A	59	7.284	51.686	-11.236	1.00	28.81	C
ATOM	466	CE	LYS	A	59	7.118	51.103	-12.636	1.00	36.29	C
ATOM	467	NZ	LYS	A	59	7.341	49.618	-12.595	1.00	41.43	N
ATOM	468	N	GLN	A	60	8.062	56.183	-7.819	1.00	20.52	N
ATOM	469	CA	GLN	A	60	8.085	56.580	-6.416	1.00	20.62	C
ATOM	470	C	GLN	A	60	7.205	57.777	-6.168	1.00	19.66	C
ATOM	471	O	GLN	A	60	7.186	58.767	-6.948	1.00	19.92	O
ATOM	472	CB	GLN	A	60	9.528	56.943	-6.031	1.00	20.76	C
ATOM	473	CG	GLN	A	60	9.658	57.320	-4.544	1.00	24.20	C
ATOM	474	CD	GLN	A	60	9.442	56.154	-3.617	1.00	25.06	C
ATOM	475	OE1	GLN	A	60	9.058	56.349	-2.451	1.00	31.15	O

FIGURE 4H

ATOM	476	NE2	GLN	A	60	9.683	54.936	-4.098	1.00	26.98	N
ATOM	477	N	GLN	A	61	6.443	57.717	-5.061	1.00	18.63	N
ATOM	478	CA	GLN	A	61	5.646	58.853	-4.656	1.00	19.20	C
ATOM	479	C	GLN	A	61	6.238	59.323	-3.329	1.00	16.91	C
ATOM	480	O	GLN	A	61	7.096	58.618	-2.792	1.00	17.73	O
ATOM	481	CB	GLN	A	61	4.152	58.480	-4.562	1.00	18.77	C
ATOM	482	CG	GLN	A	61	3.566	58.142	-5.969	1.00	26.87	C
ATOM	483	CD	GLN	A	61	2.129	57.645	-5.913	1.00	33.51	C
ATOM	484	OE1	GLN	A	61	1.336	58.080	-5.039	1.00	40.50	O
ATOM	485	NE2	GLN	A	61	1.776	56.722	-6.814	1.00	34.57	N
ATOM	486	N	ARG	A	62	5.820	60.506	-2.864	1.00	16.49	N
ATOM	487	CA	ARG	A	62	6.428	61.168	-1.704	1.00	15.26	C
ATOM	488	C	ARG	A	62	7.912	61.226	-1.901	1.00	15.96	C
ATOM	489	O	ARG	A	62	8.688	60.840	-1.002	1.00	14.67	O
ATOM	490	CB	ARG	A	62	6.064	60.472	-0.370	1.00	15.13	C
ATOM	491	CG	ARG	A	62	4.554	60.425	-0.167	1.00	16.67	C
ATOM	492	CD	ARG	A	62	4.222	60.474	1.316	1.00	17.55	C
ATOM	493	NE	ARG	A	62	4.433	59.142	1.922	1.00	17.21	N
ATOM	494	CZ	ARG	A	62	3.878	58.794	3.096	1.00	17.75	C
ATOM	495	NH1	ARG	A	62	4.068	57.592	3.620	1.00	17.79	N
ATOM	496	NH2	ARG	A	62	3.124	59.698	3.704	1.00	16.47	N
ATOM	497	N	ARG	A	63	8.346	61.685	-3.087	1.00	15.72	N
ATOM	498	CA	ARG	A	63	9.807	61.665	-3.355	1.00	13.77	C
ATOM	499	C	ARG	A	63	10.519	62.623	-2.416	1.00	14.07	C
ATOM	500	O	ARG	A	63	11.696	62.465	-2.163	1.00	13.33	O
ATOM	501	CB	ARG	A	63	10.075	62.072	-4.821	1.00	15.62	C
ATOM	502	CG	ARG	A	63	9.560	61.016	-5.747	1.00	13.62	C
ATOM	503	CD	ARG	A	63	9.451	61.482	-7.239	1.00	18.07	C
ATOM	504	NE	ARG	A	63	8.407	62.486	-7.226	1.00	19.25	N
ATOM	505	CZ	ARG	A	63	8.334	63.575	-7.995	1.00	23.67	C
ATOM	506	NH1	ARG	A	63	7.335	64.461	-7.798	1.00	25.09	N
ATOM	507	NH2	ARG	A	63	9.202	63.747	-8.988	1.00	18.57	N
ATOM	508	N	GLU	A	64	9.803	63.616	-1.909	1.00	14.50	N
ATOM	509	CA	GLU	A	64	10.407	64.556	-0.973	1.00	17.59	C
ATOM	510	C	GLU	A	64	11.009	63.830	0.228	1.00	15.22	C
ATOM	511	O	GLU	A	64	12.055	64.284	0.704	1.00	14.88	O
ATOM	512	CB	GLU	A	64	9.463	65.638	-0.466	1.00	19.82	C
ATOM	513	CG	GLU	A	64	8.210	65.187	0.284	1.00	28.36	C
ATOM	514	CD	GLU	A	64	7.064	64.624	-0.576	1.00	36.29	C
ATOM	515	OE1	GLU	A	64	7.100	64.665	-1.867	1.00	33.16	O
ATOM	516	OE2	GLU	A	64	6.096	64.115	0.084	1.00	39.40	O
ATOM	517	N	LEU	A	65	10.368	62.754	0.663	1.00	13.41	N
ATOM	518	CA	LEU	A	65	10.893	61.978	1.818	1.00	12.09	C
ATOM	519	C	LEU	A	65	12.220	61.313	1.520	1.00	13.33	C
ATOM	520	O	LEU	A	65	13.056	61.191	2.418	1.00	13.38	O
ATOM	521	CB	LEU	A	65	9.898	60.922	2.339	1.00	12.36	C
ATOM	522	CG	LEU	A	65	8.557	61.517	2.624	1.00	11.55	C
ATOM	523	CD1	LEU	A	65	7.686	60.399	3.203	1.00	15.36	C
ATOM	524	CD2	LEU	A	65	8.659	62.704	3.592	1.00	14.28	C
ATOM	525	N	LEU	A	66	12.408	60.811	0.283	1.00	13.19	N
ATOM	526	CA	LEU	A	66	13.703	60.208	-0.093	1.00	13.88	C
ATOM	527	C	LEU	A	66	14.756	61.292	-0.066	1.00	15.69	C
ATOM	528	O	LEU	A	66	15.863	61.101	0.434	1.00	14.61	O
ATOM	529	CB	LEU	A	66	13.659	59.636	-1.530	1.00	16.89	C
ATOM	530	CG	LEU	A	66	12.676	58.532	-1.843	1.00	21.31	C
ATOM	531	CD1	LEU	A	66	12.768	58.297	-3.354	1.00	24.66	C
ATOM	532	CD2	LEU	A	66	13.045	57.279	-1.076	1.00	24.73	C
ATOM	533	N	PHE	A	67	14.425	62.448	-0.646	1.00	13.46	N
ATOM	534	CA	PHE	A	67	15.345	63.567	-0.626	1.00	13.17	C
ATOM	535	C	PHE	A	67	15.754	63.942	0.811	1.00	11.21	C

FIGURE 4I

ATOM	536	O	PHE	A	67	16.916	64.092	1.130	1.00	12.87	O
ATOM	537	CB	PHE	A	67	14.685	64.774	-1.349	1.00	12.78	C
ATOM	538	CG	PHE	A	67	15.596	65.943	-1.500	1.00	15.41	C
ATOM	539	CD1	PHE	A	67	16.503	66.021	-2.595	1.00	18.19	C
ATOM	540	CE1	PHE	A	67	17.344	67.132	-2.722	1.00	18.52	C
ATOM	541	CZ	PHE	A	67	17.333	68.149	-1.763	1.00	20.79	C
ATOM	542	CE2	PHE	A	67	16.456	68.062	-0.680	1.00	20.02	C
ATOM	543	CD2	PHE	A	67	15.592	66.955	-0.568	1.00	17.30	C
ATOM	544	N	ASN	A	68	14.748	64.105	1.678	1.00	12.96	N
ATOM	545	CA	ASN	A	68	15.077	64.562	3.015	1.00	12.14	C
ATOM	546	C	ASN	A	68	15.965	63.544	3.732	1.00	11.06	C
ATOM	547	O	ASN	A	68	16.878	63.964	4.433	1.00	12.48	O
ATOM	548	CB	ASN	A	68	13.815	64.722	3.866	1.00	13.20	C
ATOM	549	CG	ASN	A	68	12.915	65.783	3.357	1.00	13.46	C
ATOM	550	OD1	ASN	A	68	13.354	66.704	2.648	1.00	16.36	O
ATOM	551	ND2	ASN	A	68	11.624	65.684	3.711	1.00	15.19	N
ATOM	552	N	GLU	A	69	15.629	62.261	3.625	1.00	10.11	N
ATOM	553	CA	GLU	A	69	16.454	61.221	4.278	1.00	12.28	C
ATOM	554	C	GLU	A	69	17.892	61.208	3.767	1.00	12.73	C
ATOM	555	O	GLU	A	69	18.809	61.075	4.538	1.00	13.29	O
ATOM	556	CB	GLU	A	69	15.839	59.813	4.105	1.00	12.61	C
ATOM	557	CG	GLU	A	69	16.573	58.779	4.932	1.00	16.50	C
ATOM	558	CD	GLU	A	69	15.914	57.453	4.867	1.00	23.66	C
ATOM	559	OE1	GLU	A	69	14.754	57.368	4.366	1.00	23.07	O
ATOM	560	OE2	GLU	A	69	16.552	56.491	5.339	1.00	23.27	O
ATOM	561	N	VAL	A	70	18.081	61.366	2.466	1.00	12.91	N
ATOM	562	CA	VAL	A	70	19.456	61.405	1.953	1.00	13.94	C
ATOM	563	C	VAL	A	70	20.187	62.627	2.457	1.00	15.67	C
ATOM	564	O	VAL	A	70	21.347	62.527	2.910	1.00	18.39	O
ATOM	565	CB	VAL	A	70	19.491	61.365	0.403	1.00	15.95	C
ATOM	566	CG1	VAL	A	70	20.933	61.689	-0.086	1.00	19.15	C
ATOM	567	CG2	VAL	A	70	18.993	59.979	-0.088	1.00	16.29	C
ATOM	568	N	VAL	A	71	19.549	63.800	2.408	1.00	13.10	N
ATOM	569	CA	VAL	A	71	20.216	65.022	2.835	1.00	15.04	C
ATOM	570	C	VAL	A	71	20.531	65.000	4.331	1.00	15.18	C
ATOM	571	O	VAL	A	71	21.597	65.419	4.766	1.00	16.38	O
ATOM	572	CB	VAL	A	71	19.327	66.231	2.539	1.00	16.36	C
ATOM	573	CG1	VAL	A	71	19.916	67.516	3.145	1.00	23.11	C
ATOM	574	CG2	VAL	A	71	19.235	66.392	1.066	1.00	20.39	C
ATOM	575	N	ILE	A	72	19.587	64.504	5.125	1.00	14.45	N
ATOM	576	CA	ILE	A	72	19.762	64.605	6.572	1.00	14.74	C
ATOM	577	C	ILE	A	72	20.658	63.509	7.069	1.00	15.25	C
ATOM	578	O	ILE	A	72	21.602	63.806	7.816	1.00	18.20	O
ATOM	579	CB	ILE	A	72	18.387	64.547	7.300	1.00	13.58	C
ATOM	580	CG1	ILE	A	72	17.574	65.759	6.893	1.00	12.87	C
ATOM	581	CD1	ILE	A	72	16.090	65.761	7.362	1.00	13.66	C
ATOM	582	CG2	ILE	A	72	18.596	64.471	8.836	1.00	14.60	C
ATOM	583	N	MET	A	73	20.398	62.254	6.694	1.00	13.90	N
ATOM	584	CA	MET	A	73	21.054	61.133	7.376	1.00	15.98	C
ATOM	585	C	MET	A	73	22.432	60.754	6.831	1.00	17.84	C
ATOM	586	O	MET	A	73	23.171	59.978	7.441	1.00	17.77	O
ATOM	587	CB	MET	A	73	20.133	59.914	7.453	1.00	15.79	C
ATOM	588	CG	MET	A	73	18.934	60.190	8.379	1.00	15.32	C
ATOM	589	SD	MET	A	73	19.392	60.663	10.070	1.00	16.30	S
ATOM	590	CE	MET	A	73	20.181	59.111	10.621	1.00	17.22	C
ATOM	591	N	ARG	A	74	22.794	61.345	5.701	1.00	18.37	N
ATOM	592	CA	ARG	A	74	24.024	60.912	5.081	1.00	22.44	C
ATOM	593	C	ARG	A	74	25.217	61.169	5.994	1.00	24.52	C
ATOM	594	O	ARG	A	74	26.097	60.311	6.104	1.00	27.75	O
ATOM	595	CB	ARG	A	74	24.206	61.518	3.686	1.00	23.00	C

FIGURE 4J

ATOM	596	CG	ARG A	74	25.480	60.985	2.929	1.00	22.74	C
ATOM	597	CD	ARG A	74	25.589	59.430	2.618	1.00	22.85	C
ATOM	598	NE	ARG A	74	26.926	59.224	2.000	1.00	25.04	N
ATOM	599	CZ	ARG A	74	28.078	59.243	2.692	1.00	26.56	C
ATOM	600	NH1	ARG A	74	29.239	59.085	2.044	1.00	25.26	N
ATOM	601	NH2	ARG A	74	28.072	59.386	4.045	1.00	24.17	N
ATOM	602	N	ASP A	75	25.230	62.299	6.685	1.00	24.42	N
ATOM	603	CA	ASP A	75	26.407	62.661	7.440	1.00	25.42	C
ATOM	604	C	ASP A	75	26.306	62.355	8.979	1.00	25.26	C
ATOM	605	O	ASP A	75	27.145	62.798	9.739	1.00	25.72	O
ATOM	606	CB	BASP A	75	26.760	64.135	7.190	0.35	26.70	C
ATOM	607	CB	AASP A	75	26.779	64.131	7.167	0.65	27.91	C
ATOM	608	N	TYR A	76	25.314	61.558	9.404	1.00	18.52	N
ATOM	609	CA	TYR A	76	25.238	61.063	10.801	1.00	17.52	C
ATOM	610	C	TYR A	76	25.571	59.569	10.854	1.00	17.12	C
ATOM	611	O	TYR A	76	25.435	58.843	9.859	1.00	19.50	O
ATOM	612	CB	TYR A	76	23.844	61.320	11.399	1.00	16.15	C
ATOM	613	CG	TYR A	76	23.529	62.809	11.478	1.00	14.46	C
ATOM	614	CD1	TYR A	76	24.370	63.681	12.192	1.00	17.70	C
ATOM	615	CE1	TYR A	76	24.118	65.077	12.233	1.00	19.31	C
ATOM	616	CZ	TYR A	76	23.011	65.608	11.567	1.00	18.49	C
ATOM	617	OH	TYR A	76	22.755	66.931	11.664	1.00	23.24	O
ATOM	618	CE2	TYR A	76	22.172	64.758	10.864	1.00	15.69	C
ATOM	619	CD2	TYR A	76	22.438	63.361	10.810	1.00	16.31	C
ATOM	620	N	GLN A	77	26.035	59.102	11.992	1.00	14.90	N
ATOM	621	CA	GLN A	77	26.266	57.664	12.136	1.00	15.54	C
ATOM	622	C	GLN A	77	26.204	57.374	13.611	1.00	14.41	C
ATOM	623	O	GLN A	77	26.785	58.118	14.406	1.00	15.81	O
ATOM	624	CB	GLN A	77	27.699	57.270	11.657	1.00	18.19	C
ATOM	625	CG	GLN A	77	28.072	55.734	11.772	1.00	23.37	C
ATOM	626	CD	GLN A	77	28.614	55.207	13.186	1.00	26.91	C
ATOM	627	OE1	GLN A	77	28.420	54.018	13.544	1.00	29.00	O
ATOM	628	NE2	GLN A	77	29.283	56.066	13.939	1.00	29.67	N
ATOM	629	N	HIS A	78	25.621	56.237	13.936	1.00	12.38	N
ATOM	630	CA	HIS A	78	25.579	55.764	15.317	1.00	9.38	C
ATOM	631	C	HIS A	78	25.341	54.265	15.321	1.00	10.65	C
ATOM	632	O	HIS A	78	24.614	53.741	14.473	1.00	12.69	O
ATOM	633	CB	HIS A	78	24.476	56.478	16.090	1.00	10.58	C
ATOM	634	CG	HIS A	78	24.413	56.104	17.540	1.00	10.93	C
ATOM	635	ND1	HIS A	78	24.958	56.900	18.537	1.00	17.77	N
ATOM	636	CE1	HIS A	78	24.770	56.316	19.705	1.00	12.73	C
ATOM	637	NE2	HIS A	78	24.127	55.176	19.501	1.00	16.66	N
ATOM	638	CD2	HIS A	78	23.880	55.024	18.154	1.00	9.48	C
ATOM	639	N	PHE A	79	25.943	53.570	16.298	1.00	12.85	N
ATOM	640	CA	PHE A	79	25.831	52.108	16.289	1.00	13.99	C
ATOM	641	C	PHE A	79	24.422	51.594	16.426	1.00	12.74	C
ATOM	642	O	PHE A	79	24.151	50.454	16.056	1.00	15.25	O
ATOM	643	CB	PHE A	79	26.697	51.436	17.375	1.00	15.70	C
ATOM	644	CG	PHE A	79	27.094	50.017	17.026	1.00	23.71	C
ATOM	645	N	ASN A	80	23.535	52.407	17.015	1.00	11.50	N
ATOM	646	CA	ASN A	80	22.168	51.992	17.211	1.00	11.01	C
ATOM	647	C	ASN A	80	21.243	52.579	16.160	1.00	10.32	C
ATOM	648	O	ASN A	80	20.039	52.607	16.335	1.00	10.59	O
ATOM	649	CB	ASN A	80	21.642	52.378	18.606	1.00	12.14	C
ATOM	650	CG	ASN A	80	22.321	51.578	19.718	1.00	15.81	C
ATOM	651	OD1	ASN A	80	22.970	52.157	20.569	1.00	23.90	O
ATOM	652	ND2	ASN A	80	22.159	50.267	19.710	1.00	19.55	N
ATOM	653	N	VAL A	81	21.814	53.065	15.039	1.00	9.07	N
ATOM	654	CA	VAL A	81	20.987	53.539	13.887	1.00	8.92	C
ATOM	655	C	VAL A	81	21.419	52.771	12.654	1.00	7.73	C

FIGURE 4K

ATOM	656	O	VAL	A	81	22.630	52.675	12.359	1.00	8.95	O
ATOM	657	CB	VAL	A	81	21.225	55.033	13.691	1.00	8.16	C
ATOM	658	CG1	VAL	A	81	20.581	55.533	12.401	1.00	10.66	C
ATOM	659	CG2	VAL	A	81	20.765	55.865	14.944	1.00	9.57	C
ATOM	660	N	VAL	A	82	20.446	52.191	11.966	1.00	8.42	N
ATOM	661	CA	VAL	A	82	20.763	51.445	10.730	1.00	7.72	C
ATOM	662	C	VAL	A	82	21.379	52.442	9.747	1.00	8.94	C
ATOM	663	O	VAL	A	82	20.759	53.483	9.413	1.00	10.35	O
ATOM	664	CB	VAL	A	82	19.494	50.833	10.165	1.00	10.01	C
ATOM	665	CG1	VAL	A	82	19.824	50.119	8.839	1.00	12.08	C
ATOM	666	CG2	VAL	A	82	18.927	49.832	11.162	1.00	12.64	C
ATOM	667	N	GLU	A	83	22.610	52.140	9.308	1.00	10.70	N
ATOM	668	CA	GLU	A	83	23.375	53.129	8.600	1.00	11.89	C
ATOM	669	C	GLU	A	83	23.089	53.185	7.122	1.00	12.81	C
ATOM	670	O	GLU	A	83	22.988	52.158	6.454	1.00	14.07	O
ATOM	671	CB	GLU	A	83	24.897	52.834	8.796	1.00	12.73	C
ATOM	672	CG	GLU	A	83	25.818	53.960	8.295	1.00	16.96	C
ATOM	673	CD	GLU	A	83	27.313	53.730	8.594	1.00	19.90	C
ATOM	674	OE1	GLU	A	83	27.704	52.860	9.444	1.00	21.39	O
ATOM	675	OE2	GLU	A	83	28.103	54.487	7.949	1.00	25.16	O
ATOM	676	N	MET	A	84	22.941	54.406	6.633	1.00	12.37	N
ATOM	677	CA	MET	A	84	22.903	54.658	5.196	1.00	13.43	C
ATOM	678	C	MET	A	84	24.289	54.957	4.729	1.00	15.27	C
ATOM	679	O	MET	A	84	24.853	56.035	5.049	1.00	15.52	O
ATOM	680	CB	MET	A	84	21.982	55.843	4.869	1.00	16.45	C
ATOM	681	CG	MET	A	84	21.993	56.101	3.361	1.00	19.85	C
ATOM	682	SD	MET	A	84	21.214	57.739	2.997	1.00	30.09	S
ATOM	683	CE	MET	A	84	19.620	57.360	3.393	1.00	27.67	C
ATOM	684	N	TYR	A	85	24.875	54.025	3.978	1.00	10.98	N
ATOM	685	CA	TYR	A	85	26.293	54.219	3.628	1.00	10.62	C
ATOM	686	C	TYR	A	85	26.504	55.208	2.511	1.00	12.33	C
ATOM	687	O	TYR	A	85	27.449	55.991	2.564	1.00	14.14	O
ATOM	688	CB	TYR	A	85	26.894	52.905	3.175	1.00	8.90	C
ATOM	689	CG	TYR	A	85	26.868	51.818	4.228	1.00	10.43	C
ATOM	690	CD1	TYR	A	85	26.306	50.570	3.911	1.00	13.38	C
ATOM	691	CE1	TYR	A	85	26.325	49.523	4.819	1.00	14.61	C
ATOM	692	CZ	TYR	A	85	26.863	49.741	6.079	1.00	13.44	C
ATOM	693	OH	TYR	A	85	26.861	48.672	6.980	1.00	17.07	O
ATOM	694	CE2	TYR	A	85	27.391	50.975	6.449	1.00	13.82	C
ATOM	695	CD2	TYR	A	85	27.397	52.033	5.477	1.00	12.40	C
ATOM	696	N	LYS	A	86	25.666	55.116	1.495	1.00	10.58	N
ATOM	697	CA	LYS	A	86	25.810	55.951	0.281	1.00	12.00	C
ATOM	698	C	LYS	A	86	24.438	56.056	-0.396	1.00	10.65	C
ATOM	699	O	LYS	A	86	23.543	55.199	-0.201	1.00	12.23	O
ATOM	700	CB	LYS	A	86	26.718	55.275	-0.739	1.00	13.28	C
ATOM	701	CG	LYS	A	86	28.193	55.033	-0.332	1.00	17.08	C
ATOM	702	CD	BLYS	A	86	29.052	56.234	-0.597	0.35	17.52	C
ATOM	703	CD	ALYS	A	86	28.985	56.308	-0.300	0.65	21.07	C
ATOM	704	CE	BLYS	A	86	30.513	55.885	-0.312	0.35	18.61	C
ATOM	705	CE	ALYS	A	86	30.434	55.995	0.074	0.65	24.99	C
ATOM	706	NZ	BLYS	A	86	30.746	55.897	1.159	0.35	17.16	N
ATOM	707	NZ	ALYS	A	86	31.288	57.208	-0.072	0.65	28.26	N
ATOM	708	N	SER	A	87	24.256	57.088	-1.209	1.00	10.03	N
ATOM	709	CA	SER	A	87	23.131	57.131	-2.122	1.00	11.42	C
ATOM	710	C	SER	A	87	23.681	57.575	-3.460	1.00	11.39	C
ATOM	711	O	SER	A	87	24.658	58.325	-3.518	1.00	11.68	O
ATOM	712	CB	SER	A	87	22.016	58.120	-1.685	1.00	12.94	C
ATOM	713	OG	SER	A	87	22.489	59.463	-1.724	1.00	20.40	O
ATOM	714	N	TYR	A	88	23.079	57.035	-4.524	1.00	10.06	N
ATOM	715	CA	TYR	A	88	23.496	57.356	-5.879	1.00	9.14	C

FIGURE 4L

ATOM	716	C	TYR	A	88	22.332	57.511	-6.793	1.00	10.75	C
ATOM	717	O	TYR	A	88	21.370	56.778	-6.676	1.00	10.73	O
ATOM	718	CB	TYR	A	88	24.364	56.167	-6.444	1.00	10.44	C
ATOM	719	CG	TYR	A	88	25.617	55.878	-5.680	1.00	9.26	C
ATOM	720	CD1	TYR	A	88	25.690	54.784	-4.828	1.00	10.69	C
ATOM	721	CE1	TYR	A	88	26.854	54.440	-4.195	1.00	13.14	C
ATOM	722	CZ	TYR	A	88	27.986	55.180	-4.392	1.00	11.93	C
ATOM	723	OH	TYR	A	88	29.125	54.804	-3.710	1.00	14.94	O
ATOM	724	CE2	TYR	A	88	27.976	56.285	-5.215	1.00	12.64	C
ATOM	725	CD2	TYR	A	88	26.777	56.608	-5.916	1.00	10.34	C
ATOM	726	N	LEU	A	89	22.448	58.437	-7.758	1.00	10.01	N
ATOM	727	CA	LEU	A	89	21.486	58.554	-8.803	1.00	11.44	C
ATOM	728	C	LEU	A	89	22.037	57.764	-9.988	1.00	13.02	C
ATOM	729	O	LEU	A	89	23.113	58.060	-10.506	1.00	15.98	O
ATOM	730	CB	LEU	A	89	21.239	60.032	-9.168	1.00	12.87	C
ATOM	731	CG	LEU	A	89	20.269	60.243	-10.313	1.00	17.18	C
ATOM	732	CD1	LEU	A	89	18.849	59.775	-9.933	1.00	16.35	C
ATOM	733	CD2	LEU	A	89	20.225	61.742	-10.559	1.00	20.37	C
ATOM	734	N	VAL	A	90	21.315	56.725	-10.360	1.00	11.48	N
ATOM	735	CA	VAL	A	90	21.732	55.741	-11.363	1.00	12.41	C
ATOM	736	C	VAL	A	90	20.692	55.685	-12.473	1.00	15.35	C
ATOM	737	O	VAL	A	90	19.701	54.981	-12.367	1.00	15.17	O
ATOM	738	CB	VAL	A	90	21.863	54.346	-10.719	1.00	13.19	C
ATOM	739	CG1	VAL	A	90	22.591	53.392	-11.649	1.00	16.49	C
ATOM	740	CG2	VAL	A	90	22.632	54.394	-9.378	1.00	13.77	C
ATOM	741	N	GLY	A	91	20.908	56.500	-13.502	1.00	18.11	N
ATOM	742	CA	GLY	A	91	19.893	56.635	-14.549	1.00	19.22	C
ATOM	743	C	GLY	A	91	18.595	57.208	-13.992	1.00	18.10	C
ATOM	744	O	GLY	A	91	18.603	58.330	-13.459	1.00	19.82	O
ATOM	745	N	GLU	A	92	17.519	56.431	-14.032	1.00	18.47	N
ATOM	746	CA	GLU	A	92	16.245	56.914	-13.492	1.00	19.58	C
ATOM	747	C	GLU	A	92	15.989	56.412	-12.083	1.00	19.05	C
ATOM	748	O	GLU	A	92	14.852	56.553	-11.585	1.00	17.35	O
ATOM	749	CB	GLU	A	92	15.067	56.434	-14.350	1.00	21.87	C
ATOM	750	CG	GLU	A	92	15.391	56.457	-15.827	1.00	25.46	C
ATOM	751	CD	GLU	A	92	15.592	57.871	-16.320	1.00	31.82	C
ATOM	752	OE1	GLU	A	92	14.979	58.815	-15.763	1.00	32.34	O
ATOM	753	OE2	GLU	A	92	16.381	58.046	-17.279	1.00	37.57	O
ATOM	754	N	GLU	A	93	16.982	55.763	-11.473	1.00	14.94	N
ATOM	755	CA	GLU	A	93	16.797	55.123	-10.199	1.00	14.61	C
ATOM	756	C	GLU	A	93	17.614	55.812	-9.145	1.00	13.21	C
ATOM	757	O	GLU	A	93	18.680	56.344	-9.429	1.00	13.71	O
ATOM	758	CB	GLU	A	93	17.226	53.656	-10.252	1.00	16.06	C
ATOM	759	CG	GLU	A	93	16.186	52.848	-11.050	1.00	18.66	C
ATOM	760	CD	GLU	A	93	16.510	51.368	-11.146	1.00	29.04	C
ATOM	761	OE1	GLU	A	93	17.633	50.963	-10.828	1.00	27.54	O
ATOM	762	OE2	GLU	A	93	15.605	50.587	-11.546	1.00	34.55	O
ATOM	763	N	LEU	A	94	17.121	55.784	-7.917	1.00	12.92	N
ATOM	764	CA	LEU	A	94	17.956	56.176	-6.790	1.00	11.80	C
ATOM	765	C	LEU	A	94	18.373	54.851	-6.147	1.00	10.79	C
ATOM	766	O	LEU	A	94	17.510	54.014	-5.822	1.00	11.95	O
ATOM	767	CB	LEU	A	94	17.138	57.024	-5.825	1.00	10.58	C
ATOM	768	CG	LEU	A	94	17.877	57.424	-4.537	1.00	14.05	C
ATOM	769	CD1	LEU	A	94	18.971	58.478	-4.809	1.00	16.12	C
ATOM	770	CD2	LEU	A	94	16.851	57.946	-3.488	1.00	16.00	C
ATOM	771	N	TRP	A	95	19.669	54.636	-5.966	1.00	9.59	N
ATOM	772	CA	TRP	A	95	20.156	53.478	-5.211	1.00	9.80	C
ATOM	773	C	TRP	A	95	20.642	53.937	-3.865	1.00	11.66	C
ATOM	774	O	TRP	A	95	21.510	54.804	-3.772	1.00	11.31	O
ATOM	775	CB	TRP	A	95	21.352	52.841	-5.946	1.00	8.99	C

FIGURE 4M

ATOM	776	CG	TRP	A	95	21.005	52.139	-7.199	1.00	9.92	C
ATOM	777	CD1	TRP	A	95	19.837	52.210	-7.928	1.00	11.08	C
ATOM	778	NE1	TRP	A	95	19.919	51.360	-9.021	1.00	13.91	N
ATOM	779	CE2	TRP	A	95	21.118	50.694	-8.983	1.00	10.77	C
ATOM	780	CD2	TRP	A	95	21.808	51.118	-7.818	1.00	10.93	C
ATOM	781	CE3	TRP	A	95	23.091	50.589	-7.541	1.00	10.76	C
ATOM	782	CZ3	TRP	A	95	23.637	49.618	-8.424	1.00	12.84	C
ATOM	783	CH2	TRP	A	95	22.936	49.217	-9.579	1.00	13.19	C
ATOM	784	CZ2	TRP	A	95	21.670	49.722	-9.891	1.00	11.91	C
ATOM	785	N	VAL	A	96	20.084	53.363	-2.801	1.00	10.54	N
ATOM	786	CA	VAL	A	96	20.513	53.688	-1.444	1.00	10.32	C
ATOM	787	C	VAL	A	96	21.142	52.452	-0.839	1.00	11.89	C
ATOM	788	O	VAL	A	96	20.511	51.404	-0.775	1.00	12.61	O
ATOM	789	CB	VAL	A	96	19.357	54.169	-0.592	1.00	11.42	C
ATOM	790	CG1	VAL	A	96	19.867	54.492	0.780	1.00	14.23	C
ATOM	791	CG2	VAL	A	96	18.719	55.422	-1.225	1.00	13.00	C
ATOM	792	N	LEU	A	97	22.391	52.556	-0.388	1.00	8.71	N
ATOM	793	CA	LEU	A	97	23.116	51.422	0.183	1.00	10.70	C
ATOM	794	C	LEU	A	97	22.986	51.457	1.712	1.00	10.07	O
ATOM	795	O	LEU	A	97	23.467	52.398	2.346	1.00	12.79	C
ATOM	796	CB	LEU	A	97	24.608	51.500	-0.135	1.00	11.16	C
ATOM	797	CG	LEU	A	97	24.997	51.138	-1.608	1.00	12.06	C
ATOM	798	CD1	LEU	A	97	24.306	51.952	-2.731	1.00	11.70	C
ATOM	799	CD2	LEU	A	97	26.521	51.215	-1.730	1.00	13.44	C
ATOM	800	N	MET	A	98	22.334	50.442	2.234	1.00	12.17	N
ATOM	801	CA	MET	A	98	22.039	50.383	3.668	1.00	11.44	C
ATOM	802	C	MET	A	98	22.786	49.232	4.354	1.00	10.59	C
ATOM	803	O	MET	A	98	23.012	48.184	3.796	1.00	12.17	O
ATOM	804	CB	MET	A	98	20.529	50.138	3.839	1.00	13.95	C
ATOM	805	CG	MET	A	98	19.666	51.320	3.245	1.00	15.96	C
ATOM	806	SD	MET	A	98	19.873	52.867	4.005	1.00	17.73	S
ATOM	807	CE	MET	A	98	19.467	52.512	5.821	1.00	14.01	C
ATOM	808	N	GLU	A	99	23.002	49.424	5.651	1.00	10.51	N
ATOM	809	CA	GLU	A	99	23.446	48.340	6.522	1.00	12.85	C
ATOM	810	C	GLU	A	99	22.388	47.190	6.464	1.00	13.14	C
ATOM	811	O	GLU	A	99	21.173	47.458	6.497	1.00	16.29	O
ATOM	812	CB	GLU	A	99	23.513	48.930	7.938	1.00	11.50	C
ATOM	813	CG	GLU	A	99	23.978	47.930	8.980	1.00	13.71	C
ATOM	814	CD	GLU	A	99	24.129	48.577	10.354	1.00	14.80	C
ATOM	815	OE1	GLU	A	99	23.869	49.794	10.534	1.00	14.64	O
ATOM	816	OE2	GLU	A	99	24.538	47.820	11.269	1.00	20.63	O
ATOM	817	N	PHE	A	100	22.836	45.933	6.370	1.00	15.63	N
ATOM	818	CA	PHE	A	100	21.921	44.810	6.215	1.00	17.57	C
ATOM	819	C	PHE	A	100	21.774	44.021	7.536	1.00	16.72	C
ATOM	820	O	PHE	A	100	22.795	43.549	8.083	1.00	20.12	O
ATOM	821	CB	PHE	A	100	22.528	43.913	5.161	1.00	20.23	C
ATOM	822	CG	PHE	A	100	21.805	42.626	4.976	1.00	22.59	C
ATOM	823	CD1	PHE	A	100	22.520	41.412	4.948	1.00	26.73	C
ATOM	824	CE1	PHE	A	100	21.844	40.202	4.750	1.00	25.39	C
ATOM	825	CZ	PHE	A	100	20.471	40.194	4.590	1.00	26.43	C
ATOM	826	CE2	PHE	A	100	19.757	41.397	4.624	1.00	26.96	C
ATOM	827	CD2	PHE	A	100	20.439	42.605	4.809	1.00	24.65	C
ATOM	828	N	LEU	A	101	20.563	43.960	8.094	1.00	18.25	N
ATOM	829	CA	LEU	A	101	20.353	43.356	9.407	1.00	18.61	C
ATOM	830	C	LEU	A	101	19.393	42.184	9.140	1.00	19.89	C
ATOM	831	O	LEU	A	101	18.500	42.308	8.268	1.00	21.24	O
ATOM	832	CB	LEU	A	101	19.656	44.318	10.379	1.00	20.99	C
ATOM	833	CG	LEU	A	101	20.524	45.270	11.230	1.00	23.61	C
ATOM	834	CD1	LEU	A	101	21.032	46.356	10.383	1.00	23.70	C
ATOM	835	CD2	LEU	A	101	19.701	45.885	12.379	1.00	24.57	C

FIGURE 4N

ATOM	836	N	GLN A 102	19.551	41.073	9.868	1.00	19.23	N
ATOM	837	CA	GLN A 102	18.779	39.866	9.580	1.00	20.33	C
ATOM	838	C	GLN A 102	17.863	39.376	10.711	1.00	20.08	C
ATOM	839	O	GLN A 102	17.265	38.275	10.629	1.00	21.98	O
ATOM	840	CB	GLN A 102	19.727	38.730	9.188	1.00	21.58	C
ATOM	841	CG	GLN A 102	20.379	39.009	7.841	1.00	25.20	C
ATOM	842	CD	GLN A 102	21.359	37.908	7.455	1.00	28.51	C
ATOM	843	OE1	GLN A 102	20.941	36.873	6.951	1.00	30.63	O
ATOM	844	NE2	GLN A 102	22.652	38.151	7.677	1.00	25.83	N
ATOM	845	N	GLY A 103	17.760	40.146	11.781	1.00	20.33	N
ATOM	846	CA	GLY A 103	16.963	39.696	12.927	1.00	19.80	C
ATOM	847	C	GLY A 103	15.505	40.121	12.956	1.00	21.24	C
ATOM	848	O	GLY A 103	14.836	39.860	13.968	1.00	21.18	O
ATOM	849	N	GLY A 104	14.990	40.753	11.905	1.00	18.61	N
ATOM	850	CA	GLY A 104	13.564	41.066	11.840	1.00	18.70	C
ATOM	851	C	GLY A 104	13.307	42.394	12.540	1.00	19.18	C
ATOM	852	O	GLY A 104	14.262	43.057	12.938	1.00	19.97	O
ATOM	853	N	ALA A 105	12.038	42.760	12.640	1.00	16.72	N
ATOM	854	CA	ALA A 105	11.601	43.969	13.322	1.00	16.50	C
ATOM	855	C	ALA A 105	11.145	43.569	14.705	1.00	16.01	C
ATOM	856	O	ALA A 105	10.696	42.427	14.975	1.00	15.11	O
ATOM	857	CB	ALA A 105	10.500	44.607	12.582	1.00	17.50	C
ATOM	858	N	LEU A 106	11.223	44.534	15.606	1.00	13.34	N
ATOM	859	CA	LEU A 106	10.767	44.272	16.948	1.00	14.34	C
ATOM	860	C	LEU A 106	9.315	43.833	17.011	1.00	13.11	C
ATOM	861	O	LEU A 106	8.947	42.998	17.849	1.00	12.50	O
ATOM	862	CB	LEU A 106	10.991	45.535	17.785	1.00	13.09	C
ATOM	863	CG	LEU A 106	10.519	45.507	19.222	1.00	15.51	C
ATOM	864	CD1	LEU A 106	11.398	44.527	20.038	1.00	16.20	C
ATOM	865	CD2	LEU A 106	10.507	46.936	19.840	1.00	13.89	C
ATOM	866	N	THR A 107	8.496	44.360	16.114	1.00	11.69	N
ATOM	867	CA	THR A 107	7.080	44.016	16.042	1.00	13.42	C
ATOM	868	C	THR A 107	6.895	42.510	15.948	1.00	14.04	C
ATOM	869	O	THR A 107	5.912	42.004	16.454	1.00	14.96	O
ATOM	870	CB	THR A 107	6.471	44.591	14.811	1.00	15.46	C
ATOM	871	OG1	THR A 107	6.652	46.008	14.805	1.00	17.52	O
ATOM	872	CG2	THR A 107	4.938	44.422	14.879	1.00	17.25	C
ATOM	873	N	ASP A 108	7.820	41.827	15.284	1.00	14.15	N
ATOM	874	CA	ASP A 108	7.698	40.361	15.109	1.00	16.22	C
ATOM	875	C	ASP A 108	7.667	39.624	16.465	1.00	15.49	C
ATOM	876	O	ASP A 108	6.996	38.587	16.601	1.00	18.94	O
ATOM	877	CB	ASP A 108	8.901	39.792	14.309	1.00	19.52	C
ATOM	878	CG	ASP A 108	9.074	40.431	12.897	1.00	26.35	C
ATOM	879	OD1	ASP A 108	8.076	41.014	12.373	1.00	26.64	O
ATOM	880	OD2	ASP A 108	10.186	40.370	12.254	1.00	29.49	O
ATOM	881	N	ILE A 109	8.379	40.157	17.449	1.00	14.12	N
ATOM	882	CA	ILE A 109	8.395	39.523	18.779	1.00	12.58	C
ATOM	883	C	ILE A 109	7.299	40.179	19.637	1.00	14.03	C
ATOM	884	O	ILE A 109	6.542	39.477	20.294	1.00	14.42	O
ATOM	885	CB	ILE A 109	9.755	39.725	19.411	1.00	14.89	C
ATOM	886	CG1	ILE A 109	10.881	39.025	18.639	1.00	14.73	C
ATOM	887	CD1	ILE A 109	12.243	39.586	19.093	1.00	17.44	C
ATOM	888	CG2	ILE A 109	9.705	39.355	20.914	1.00	14.47	C
ATOM	889	N	VAL A 110	7.169	41.499	19.637	1.00	13.45	N
ATOM	890	CA	VAL A 110	6.271	42.132	20.616	1.00	14.46	C
ATOM	891	C	VAL A 110	4.789	41.918	20.321	1.00	13.96	C
ATOM	892	O	VAL A 110	3.955	41.987	21.191	1.00	14.33	O
ATOM	893	CB	BVAL A 110	6.612	43.655	20.860	0.20	13.68	C
ATOM	894	CB	AVAL A 110	6.615	43.651	20.865	0.80	15.82	C
ATOM	895	CG1	BVAL A 110	6.986	44.373	19.601	0.20	13.60	C

FIGURE 4O

ATOM	896	CG1AVAL A 110	8.037	43.773	21.376	0.80	13.25	C
ATOM	897	CG2BVAL A 110	5.458	44.355	21.494	0.20	9.23	C
ATOM	898	CG2AVAL A 110	6.340	44.478	19.668	0.80	18.00	C
ATOM	899	N SER A 111	4.476	41.576	19.083	1.00	14.00	N
ATOM	900	CA SER A 111	3.108	41.251	18.722	1.00	15.03	C
ATOM	901	C SER A 111	2.754	39.866	19.310	1.00	16.28	C
ATOM	902	O SER A 111	1.558	39.547	19.477	1.00	19.72	O
ATOM	903	CB SER A 111	2.890	41.168	17.192	1.00	16.85	C
ATOM	904	OG SER A 111	3.677	40.164	16.557	1.00	18.09	O
ATOM	905	N GLN A 112	3.774	39.074	19.608	1.00	12.16	N
ATOM	906	CA GLN A 112	3.493	37.654	20.054	1.00	14.39	C
ATOM	907	C GLN A 112	3.735	37.415	21.536	1.00	13.10	C
ATOM	908	O GLN A 112	3.137	36.481	22.148	1.00	12.32	O
ATOM	909	CB GLN A 112	4.447	36.732	19.317	1.00	14.74	C
ATOM	910	CG GLN A 112	4.246	36.633	17.829	1.00	19.33	C
ATOM	911	CD GLN A 112	2.871	36.139	17.496	1.00	29.23	C
ATOM	912	OE1 GLN A 112	2.476	35.032	17.885	1.00	31.05	O
ATOM	913	NE2 GLN A 112	2.099	36.984	16.793	1.00	35.47	N
ATOM	914	N VAL A 113	4.690	38.155	22.089	1.00	11.18	N
ATOM	915	CA VAL A 113	5.174	37.860	23.440	1.00	12.50	C
ATOM	916	C VAL A 113	5.173	39.156	24.271	1.00	12.74	C
ATOM	917	O VAL A 113	5.397	40.268	23.727	1.00	13.07	O
ATOM	918	CB BVAL A 113	6.569	37.210	23.476	0.35	12.64	C
ATOM	919	CB AVAL A 113	6.622	37.321	23.264	0.65	14.43	C
ATOM	920	CG1BVAL A 113	7.671	38.196	23.168	0.35	9.49	C
ATOM	921	CG1AVAL A 113	7.479	37.408	24.499	0.65	13.75	C
ATOM	922	CG2BVAL A 113	6.815	36.623	24.792	0.35	12.61	C
ATOM	923	CG2AVAL A 113	6.597	35.866	22.671	0.65	11.45	C
ATOM	924	N ARG A 114	4.990	38.995	25.576	1.00	13.42	N
ATOM	925	CA ARG A 114	5.169	40.085	26.526	1.00	13.22	C
ATOM	926	C ARG A 114	6.594	40.016	27.072	1.00	13.70	C
ATOM	927	O ARG A 114	6.975	39.124	27.916	1.00	17.07	O
ATOM	928	CB ARG A 114	4.171	39.973	27.705	1.00	14.53	C
ATOM	929	CG ARG A 114	2.761	39.897	27.218	1.00	12.79	C
ATOM	930	CD ARG A 114	2.236	41.222	26.526	1.00	13.98	C
ATOM	931	NE ARG A 114	2.475	41.210	25.057	1.00	17.63	N
ATOM	932	CZ ARG A 114	1.727	40.551	24.168	1.00	17.46	C
ATOM	933	NH1 ARG A 114	0.647	39.829	24.543	1.00	22.66	N
ATOM	934	NH2 ARG A 114	2.031	40.550	22.886	1.00	18.52	N
ATOM	935	N LEU A 115	7.439	40.935	26.629	1.00	14.08	N
ATOM	936	CA LEU A 115	8.831	40.947	27.105	1.00	12.65	C
ATOM	937	C LEU A 115	8.898	41.228	28.620	1.00	12.48	C
ATOM	938	O LEU A 115	8.058	41.912	29.158	1.00	14.22	O
ATOM	939	CB LEU A 115	9.650	42.025	26.392	1.00	13.13	C
ATOM	940	CG LEU A 115	9.763	41.876	24.875	1.00	13.97	C
ATOM	941	CD1 LEU A 115	10.551	43.147	24.410	1.00	17.02	C
ATOM	942	CD2 LEU A 115	10.514	40.606	24.508	1.00	17.74	C
ATOM	943	N ASN A 116	9.932	40.695	29.254	1.00	11.88	N
ATOM	944	CA ASN A 116	10.060	40.986	30.671	1.00	13.02	C
ATOM	945	C ASN A 116	10.815	42.310	30.824	1.00	13.59	C
ATOM	946	O ASN A 116	11.244	42.912	29.813	1.00	13.07	O
ATOM	947	CB ASN A 116	10.755	39.840	31.395	1.00	16.25	C
ATOM	948	CG ASN A 116	12.178	39.630	30.919	1.00	16.11	C
ATOM	949	OD1 ASN A 116	12.912	40.583	30.657	1.00	16.01	O
ATOM	950	ND2 ASN A 116	12.584	38.368	30.826	1.00	21.99	N
ATOM	951	N GLU A 117	10.992	42.764	32.058	1.00	12.79	N
ATOM	952	CA GLU A 117	11.524	44.107	32.248	1.00	14.09	C
ATOM	953	C GLU A 117	12.974	44.282	31.789	1.00	13.32	C
ATOM	954	O GLU A 117	13.362	45.371	31.286	1.00	13.03	O
ATOM	955	CB GLU A 117	11.301	44.616	33.687	1.00	16.70	C

FIGURE 4P

ATOM	956	CG	GLU	A	117	9.822	44.855	33.942	1.00	17.78	C
ATOM	957	CD	GLU	A	117	9.496	45.727	35.155	1.00	22.57	C
ATOM	958	OE1	GLU	A	117	10.415	46.413	35.663	1.00	21.12	O
ATOM	959	OE2	GLU	A	117	8.280	45.740	35.514	1.00	20.72	O
ATOM	960	N	GLU	A	118	13.805	43.246	31.966	1.00	13.65	N
ATOM	961	CA	GLU	A	118	15.185	43.297	31.493	1.00	13.25	C
ATOM	962	C	GLU	A	118	15.205	43.439	29.944	1.00	12.90	C
ATOM	963	O	GLU	A	118	15.994	44.230	29.403	1.00	13.31	O
ATOM	964	CB	GLU	A	118	15.930	42.022	31.923	1.00	15.38	C
ATOM	965	CG	GLU	A	118	17.316	41.891	31.323	1.00	19.94	C
ATOM	966	CD	GLU	A	118	18.054	40.623	31.761	1.00	30.39	C
ATOM	967	OE1	GLU	A	118	17.496	39.489	31.672	1.00	34.33	O
ATOM	968	OE2	GLU	A	118	19.224	40.779	32.143	1.00	34.76	O
ATOM	969	N	GLN	A	119	14.334	42.696	29.268	1.00	12.94	N
ATOM	970	CA	GLN	A	119	14.252	42.787	27.785	1.00	11.65	C
ATOM	971	C	GLN	A	119	13.730	44.154	27.340	1.00	12.55	C
ATOM	972	O	GLN	A	119	14.241	44.771	26.374	1.00	11.34	O
ATOM	973	CB	GLN	A	119	13.317	41.695	27.264	1.00	13.15	C
ATOM	974	CG	GLN	A	119	13.969	40.277	27.440	1.00	13.95	C
ATOM	975	CD	GLN	A	119	13.001	39.129	27.285	1.00	15.25	C
ATOM	976	OE1	GLN	A	119	11.797	39.235	27.605	1.00	16.66	O
ATOM	977	NE2	GLN	A	119	13.523	37.999	26.756	1.00	19.76	N
ATOM	978	N	ILE	A	120	12.717	44.654	28.044	1.00	10.51	N
ATOM	979	CA	ILE	A	120	12.262	46.026	27.757	1.00	10.70	C
ATOM	980	C	ILE	A	120	13.369	47.045	27.916	1.00	11.15	C
ATOM	981	O	ILE	A	120	13.542	47.935	27.036	1.00	11.61	O
ATOM	982	CB	ILE	A	120	10.996	46.368	28.587	1.00	10.60	C
ATOM	983	CG1	ILE	A	120	9.854	45.455	28.172	1.00	12.60	C
ATOM	984	CD1	ILE	A	120	8.564	45.667	29.005	1.00	13.91	C
ATOM	985	CG2	ILE	A	120	10.604	47.889	28.445	1.00	10.56	C
ATOM	986	N	ALA	A	121	14.123	46.968	29.015	1.00	11.01	N
ATOM	987	CA	ALA	A	121	15.204	47.921	29.276	1.00	10.58	C
ATOM	988	C	ALA	A	121	16.260	47.791	28.170	1.00	11.46	C
ATOM	989	O	ALA	A	121	16.842	48.772	27.763	1.00	12.49	O
ATOM	990	CB	ALA	A	121	15.809	47.618	30.670	1.00	10.64	C
ATOM	991	N	THR	A	122	16.523	46.568	27.688	1.00	12.37	N
ATOM	992	CA	THR	A	122	17.567	46.410	26.680	1.00	13.42	C
ATOM	993	C	THR	A	122	17.115	47.147	25.395	1.00	11.43	C
ATOM	994	O	THR	A	122	17.910	47.873	24.736	1.00	13.23	O
ATOM	995	CB	THR	A	122	17.699	44.933	26.395	1.00	14.45	C
ATOM	996	OG1	THR	A	122	18.243	44.306	27.568	1.00	18.68	O
ATOM	997	CG2	THR	A	122	18.716	44.685	25.259	1.00	17.22	C
ATOM	998	N	VAL	A	123	15.818	47.003	25.066	1.00	8.58	N
ATOM	999	CA	VAL	A	123	15.303	47.707	23.861	1.00	9.31	C
ATOM	1000	C	VAL	A	123	15.329	49.203	24.073	1.00	10.75	C
ATOM	1001	O	VAL	A	123	15.818	49.976	23.213	1.00	10.05	O
ATOM	1002	CB	VAL	A	123	13.913	47.274	23.522	1.00	12.89	C
ATOM	1003	CG1	VAL	A	123	13.324	48.101	22.408	1.00	12.01	C
ATOM	1004	CG2	VAL	A	123	13.923	45.811	23.127	1.00	12.38	C
ATOM	1005	N	CYS	A	124	14.773	49.636	25.204	1.00	9.98	N
ATOM	1006	CA	CYS	A	124	14.736	51.059	25.488	1.00	11.10	C
ATOM	1007	C	CYS	A	124	16.090	51.731	25.543	1.00	11.85	C
ATOM	1008	O	CYS	A	124	16.248	52.864	25.007	1.00	12.25	O
ATOM	1009	CB	CYS	A	124	14.010	51.291	26.817	1.00	13.17	C
ATOM	1010	SG	CYS	A	124	12.233	51.061	26.610	1.00	21.75	S
ATOM	1011	N	GLU	A	125	17.066	51.098	26.189	1.00	11.05	N
ATOM	1012	CA	GLU	A	125	18.381	51.711	26.272	1.00	12.60	C
ATOM	1013	C	GLU	A	125	18.982	51.901	24.871	1.00	12.30	C
ATOM	1014	O	GLU	A	125	19.557	52.952	24.578	1.00	11.09	O
ATOM	1015	CB	GLU	A	125	19.288	50.853	27.129	1.00	14.58	C

FIGURE 4Q

ATOM	1016	CG	GLU	A	125	20.574	51.581	27.491	1.00 18.53	C
ATOM	1017	CD	GLU	A	125	21.721	51.337	26.561	1.00 27.54	C
ATOM	1018	OE1	GLU	A	125	22.764	52.003	26.829	1.00 34.34	O
ATOM	1019	OE2	GLU	A	125	21.658	50.527	25.580	1.00 30.51	O
ATOM	1020	N	ALA	A	126	18.798	50.897	23.995	1.00 9.99	N
ATOM	1021	CA	ALA	A	126	19.358	51.057	22.661	1.00 11.65	C
ATOM	1022	C	ALA	A	126	18.708	52.196	21.884	1.00 10.07	C
ATOM	1023	O	ALA	A	126	19.410	53.039	21.271	1.00 10.91	O
ATOM	1024	CB	ALA	A	126	19.276	49.706	21.918	1.00 12.17	C
ATOM	1025	N	VAL	A	127	17.368	52.230	21.914	1.00 9.33	N
ATOM	1026	CA	VAL	A	127	16.635	53.312	21.227	1.00 11.04	C
ATOM	1027	C	VAL	A	127	16.995	54.683	21.776	1.00 10.47	C
ATOM	1028	O	VAL	A	127	17.197	55.639	21.018	1.00 9.96	O
ATOM	1029	CB	VAL	A	127	15.091	53.106	21.274	1.00 11.82	C
ATOM	1030	CG1	VAL	A	127	14.347	54.254	20.562	1.00 14.40	C
ATOM	1031	CG2	VAL	A	127	14.804	51.749	20.632	1.00 13.92	C
ATOM	1032	N	LEU	A	128	17.171	54.746	23.083	1.00 8.83	N
ATOM	1033	CA	LEU	A	128	17.474	56.025	23.714	1.00 10.84	C
ATOM	1034	C	LEU	A	128	18.893	56.513	23.439	1.00 9.60	C
ATOM	1035	O	LEU	A	128	19.114	57.695	23.361	1.00 11.82	O
ATOM	1036	CB	LEU	A	128	17.216	55.917	25.222	1.00 9.40	C
ATOM	1037	CG	LEU	A	128	15.698	56.031	25.513	1.00 10.65	C
ATOM	1038	CD1	LEU	A	128	15.467	55.525	26.964	1.00 11.89	C
ATOM	1039	CD2	LEU	A	128	15.140	57.454	25.350	1.00 10.29	C
ATOM	1040	N	GLN	A	129	19.808	55.555	23.275	1.00 9.77	N
ATOM	1041	CA	GLN	A	129	21.185	55.944	22.883	1.00 12.07	C
ATOM	1042	C	GLN	A	129	21.111	56.551	21.480	1.00 11.57	C
ATOM	1043	O	GLN	A	129	21.743	57.601	21.246	1.00 11.49	O
ATOM	1044	CB	GLN	A	129	22.133	54.743	22.864	1.00 11.08	C
ATOM	1045	CG	GLN	A	129	22.500	54.232	24.258	1.00 13.59	C
ATOM	1046	CD	GLN	A	129	23.396	55.167	25.085	1.00 20.05	C
ATOM	1047	OE1	GLN	A	129	23.883	56.220	24.620	1.00 21.69	O
ATOM	1048	NE2	GLN	A	129	23.612	54.764	26.349	1.00 22.68	N
ATOM	1049	N	ALA	A	130	20.366	55.905	20.562	1.00 9.60	N
ATOM	1050	CA	ALA	A	130	20.193	56.500	19.227	1.00 10.55	C
ATOM	1051	C	ALA	A	130	19.541	57.865	19.329	1.00 11.18	C
ATOM	1052	O	ALA	A	130	19.983	58.783	18.673	1.00 9.99	O
ATOM	1053	CB	ALA	A	130	19.289	55.613	18.389	1.00 11.03	C
ATOM	1054	N	LEU	A	131	18.440	57.982	20.101	1.00 9.86	N
ATOM	1055	CA	LEU	A	131	17.715	59.267	20.132	1.00 11.73	C
ATOM	1056	C	LEU	A	131	18.551	60.354	20.831	1.00 10.68	C
ATOM	1057	O	LEU	A	131	18.490	61.531	20.430	1.00 12.36	O
ATOM	1058	CB	LEU	A	131	16.342	59.123	20.818	1.00 10.06	C
ATOM	1059	CG	LEU	A	131	15.315	58.296	20.058	1.00 11.70	C
ATOM	1060	CD1	LEU	A	131	14.019	58.206	20.940	1.00 13.25	C
ATOM	1061	CD2	LEU	A	131	14.988	58.876	18.660	1.00 12.48	C
ATOM	1062	N	ALA	A	132	19.285	60.016	21.885	1.00 10.23	N
ATOM	1063	CA	ALA	A	132	20.089	61.034	22.526	1.00 12.26	C
ATOM	1064	C	ALA	A	132	21.138	61.598	21.531	1.00 13.96	C
ATOM	1065	O	ALA	A	132	21.355	62.791	21.492	1.00 14.29	O
ATOM	1066	CB	ALA	A	132	20.729	60.513	23.780	1.00 14.33	C
ATOM	1067	N	TYR	A	133	21.704	60.720	20.695	1.00 11.05	N
ATOM	1068	CA	TYR	A	133	22.659	61.221	19.697	1.00 11.87	C
ATOM	1069	C	TYR	A	133	21.934	62.028	18.610	1.00 11.09	C
ATOM	1070	O	TYR	A	133	22.345	63.138	18.302	1.00 12.95	O
ATOM	1071	CB	TYR	A	133	23.327	59.995	19.048	1.00 11.95	C
ATOM	1072	CG	TYR	A	133	24.049	60.316	17.758	1.00 13.87	C
ATOM	1073	CD1	TYR	A	133	25.280	60.927	17.782	1.00 17.00	C
ATOM	1074	CE1	TYR	A	133	25.962	61.218	16.562	1.00 13.99	C
ATOM	1075	CZ	TYR	A	133	25.389	60.899	15.362	1.00 16.47	C

FIGURE 4R

ATOM	1076	OH	TYR	A	133	26.060	61.202	14.166	1.00	17.81	O
ATOM	1077	CE2	TYR	A	133	24.146	60.298	15.294	1.00	16.35	C
ATOM	1078	CD2	TYR	A	133	23.472	59.992	16.529	1.00	16.98	C
ATOM	1079	N	LEU	A	134	20.841	61.498	18.074	1.00	9.47	N
ATOM	1080	CA	LEU	A	134	20.146	62.211	17.011	1.00	10.45	C
ATOM	1081	C	LEU	A	134	19.607	63.569	17.506	1.00	9.46	C
ATOM	1082	O	LEU	A	134	19.713	64.570	16.803	1.00	8.97	O
ATOM	1083	CB	LEU	A	134	18.986	61.378	16.461	1.00	10.59	C
ATOM	1084	CG	LEU	A	134	19.390	60.088	15.671	1.00	13.02	C
ATOM	1085	CD1	LEU	A	134	18.117	59.366	15.470	1.00	17.36	C
ATOM	1086	CD2	LEU	A	134	20.068	60.420	14.337	1.00	15.31	C
ATOM	1087	N	HIS	A	135	18.974	63.598	18.694	1.00	9.56	N
ATOM	1088	CA	HIS	A	135	18.362	64.855	19.167	1.00	8.61	C
ATOM	1089	C	HIS	A	135	19.442	65.910	19.447	1.00	11.06	C
ATOM	1090	O	HIS	A	135	19.190	67.096	19.208	1.00	11.37	O
ATOM	1091	CB	HIS	A	135	17.569	64.593	20.429	1.00	8.92	C
ATOM	1092	CG	HIS	A	135	16.299	63.823	20.243	1.00	9.30	C
ATOM	1093	ND1	HIS	A	135	15.760	63.385	19.029	1.00	11.41	N
ATOM	1094	CE1	HIS	A	135	14.617	62.724	19.257	1.00	4.33	C
ATOM	1095	NE2	HIS	A	135	14.460	62.662	20.574	1.00	10.92	N
ATOM	1096	CD2	HIS	A	135	15.512	63.295	21.207	1.00	4.45	C
ATOM	1097	N	ALA	A	136	20.615	65.465	19.884	1.00	11.25	N
ATOM	1098	CA	ALA	A	136	21.706	66.411	20.124	1.00	13.83	C
ATOM	1099	C	ALA	A	136	22.157	67.029	18.794	1.00	15.27	C
ATOM	1100	O	ALA	A	136	22.751	68.103	18.790	1.00	16.71	O
ATOM	1101	CB	ALA	A	136	22.886	65.666	20.784	1.00	14.20	C
ATOM	1102	N	GLN	A	137	21.949	66.337	17.683	1.00	11.54	N
ATOM	1103	CA	GLN	A	137	22.295	66.900	16.378	1.00	14.15	C
ATOM	1104	C	GLN	A	137	21.189	67.700	15.758	1.00	13.56	C
ATOM	1105	O	GLN	A	137	21.338	68.246	14.642	1.00	15.91	O
ATOM	1106	CB	GLN	A	137	22.698	65.761	15.397	1.00	12.79	C
ATOM	1107	CG	GLN	A	137	23.845	64.869	15.910	1.00	17.58	C
ATOM	1108	CD	GLN	A	137	25.051	65.726	16.199	1.00	26.69	C
ATOM	1109	OE1	GLN	A	137	25.471	66.464	15.339	1.00	28.56	O
ATOM	1110	NE2	GLN	A	137	25.540	65.700	17.407	1.00	33.40	N
ATOM	1111	N	GLY	A	138	20.026	67.730	16.401	1.00	10.42	N
ATOM	1112	CA	GLY	A	138	18.814	68.377	15.872	1.00	10.42	C
ATOM	1113	C	GLY	A	138	17.966	67.535	14.915	1.00	10.09	C
ATOM	1114	O	GLY	A	138	17.151	68.068	14.153	1.00	12.40	O
ATOM	1115	N	VAL	A	139	18.163	66.213	14.940	1.00	9.19	N
ATOM	1116	CA	VAL	A	139	17.370	65.368	14.097	1.00	8.77	C
ATOM	1117	C	VAL	A	139	16.173	64.854	14.886	1.00	9.95	C
ATOM	1118	O	VAL	A	139	16.379	64.338	16.011	1.00	10.76	O
ATOM	1119	CB	VAL	A	139	18.196	64.171	13.579	1.00	9.06	C
ATOM	1120	CG1	VAL	A	139	17.301	63.283	12.734	1.00	10.36	C
ATOM	1121	CG2	VAL	A	139	19.375	64.725	12.704	1.00	10.69	C
ATOM	1122	N	ILE	A	140	14.980	64.973	14.279	1.00	9.20	N
ATOM	1123	CA	ILE	A	140	13.752	64.365	14.822	1.00	7.17	C
ATOM	1124	C	ILE	A	140	13.357	63.214	13.920	1.00	7.49	C
ATOM	1125	O	ILE	A	140	13.270	63.378	12.727	1.00	8.88	O
ATOM	1126	CB	ILE	A	140	12.600	65.368	14.877	1.00	8.02	C
ATOM	1127	CG1	ILE	A	140	13.089	66.760	15.341	1.00	12.50	C
ATOM	1128	CD1	ILE	A	140	11.964	67.797	15.176	1.00	12.44	C
ATOM	1129	CG2	ILE	A	140	11.477	64.797	15.824	1.00	11.12	C
ATOM	1130	N	HIS	A	141	13.109	62.067	14.507	1.00	7.87	N
ATOM	1131	CA	HIS	A	141	12.819	60.886	13.654	1.00	6.03	C
ATOM	1132	C	HIS	A	141	11.374	60.937	13.144	1.00	7.50	C
ATOM	1133	O	HIS	A	141	11.113	60.735	11.943	1.00	8.21	O
ATOM	1134	CB	HIS	A	141	13.058	59.635	14.508	1.00	8.33	C
ATOM	1135	CG	HIS	A	141	12.795	58.362	13.763	1.00	8.10	C

FIGURE 4S

ATOM	1136	ND1 HIS A 141	11.537	57.884	13.505	1.00	8.17	N
ATOM	1137	CE1 HIS A 141	11.625	56.727	12.869	1.00	10.41	C
ATOM	1138	NE2 HIS A 141	12.914	56.456	12.664	1.00	9.43	N
ATOM	1139	CD2 HIS A 141	13.663	57.446	13.242	1.00	10.16	C
ATOM	1140	N ARG A 142	10.434	61.155	14.066	1.00	7.54	N
ATOM	1141	CA ARG A 142	9.028	61.421	13.769	1.00	7.41	C
ATOM	1142	C ARG A 142	8.201	60.196	13.394	1.00	9.29	C
ATOM	1143	O ARG A 142	6.966	60.333	13.154	1.00	10.59	O
ATOM	1144	CB ARG A 142	8.780	62.549	12.720	1.00	8.27	C
ATOM	1145	CG ARG A 142	9.477	63.832	13.191	1.00	9.10	C
ATOM	1146	CD ARG A 142	8.944	65.110	12.507	1.00	9.42	C
ATOM	1147	NE ARG A 142	9.181	65.052	11.064	1.00	8.94	N
ATOM	1148	CZ ARG A 142	8.923	66.088	10.283	1.00	9.87	C
ATOM	1149	NH1 ARG A 142	9.200	66.030	8.976	1.00	12.02	N
ATOM	1150	NH2 ARG A 142	8.336	67.162	10.803	1.00	10.46	N
ATOM	1151	N ASP A 143	8.824	59.026	13.407	1.00	7.57	N
ATOM	1152	CA ASP A 143	8.023	57.801	13.145	1.00	8.88	C
ATOM	1153	C ASP A 143	8.442	56.632	13.987	1.00	10.57	C
ATOM	1154	O ASP A 143	8.513	55.482	13.489	1.00	12.58	O
ATOM	1155	CB ASP A 143	8.002	57.503	11.632	1.00	11.13	C
ATOM	1156	CG ASP A 143	6.764	56.723	11.212	1.00	18.83	C
ATOM	1157	OD1 ASP A 143	5.776	56.605	12.004	1.00	17.51	O
ATOM	1158	OD2 ASP A 143	6.743	56.154	10.072	1.00	20.61	O
ATOM	1159	N ILE A 144	8.683	56.896	15.290	1.00	10.10	N
ATOM	1160	CA ILE A 144	9.100	55.832	16.210	1.00	9.71	C
ATOM	1161	C ILE A 144	7.882	54.910	16.530	1.00	11.44	C
ATOM	1162	O ILE A 144	6.779	55.385	16.846	1.00	10.40	O
ATOM	1163	CB ILE A 144	9.662	56.452	17.514	1.00	11.81	C
ATOM	1164	CG1BILE A 144	10.926	57.236	17.117	0.35	10.81	C
ATOM	1165	CG1AILE A 144	10.943	57.284	17.241	0.65	12.58	C
ATOM	1166	CD1BILE A 144	11.635	57.844	18.199	0.35	9.54	C
ATOM	1167	CD1AILE A 144	12.122	56.415	16.843	0.65	15.04	C
ATOM	1168	CG2 ILE A 144	9.934	55.350	18.559	1.00	12.62	C
ATOM	1169	N LYS A 145	8.090	53.602	16.360	1.00	9.50	N
ATOM	1170	CA LYS A 145	7.082	52.559	16.692	1.00	9.17	C
ATOM	1171	C LYS A 145	7.804	51.250	16.566	1.00	10.72	C
ATOM	1172	O LYS A 145	8.917	51.209	16.025	1.00	9.64	O
ATOM	1173	CB LYS A 145	5.942	52.610	15.707	1.00	10.43	C
ATOM	1174	CG LYS A 145	6.379	52.552	14.271	1.00	11.59	C
ATOM	1175	CD LYS A 145	5.155	52.746	13.355	1.00	17.86	C
ATOM	1176	CE LYS A 145	5.526	53.157	11.919	1.00	23.57	C
ATOM	1177	NZ LYS A 145	6.741	52.617	11.308	1.00	26.05	N
ATOM	1178	N SER A 146	7.176	50.139	16.981	1.00	11.26	N
ATOM	1179	CA SER A 146	7.930	48.908	17.042	1.00	11.22	C
ATOM	1180	C SER A 146	8.431	48.424	15.721	1.00	11.43	C
ATOM	1181	O SER A 146	9.457	47.733	15.689	1.00	12.31	O
ATOM	1182	CB SER A 146	7.032	47.781	17.660	1.00	10.91	C
ATOM	1183	OG SER A 146	5.827	47.616	16.911	1.00	14.55	O
ATOM	1184	N ASP A 147	7.758	48.778	14.632	1.00	10.74	N
ATOM	1185	CA ASP A 147	8.286	48.268	13.378	1.00	13.24	C
ATOM	1186	C ASP A 147	9.360	49.125	12.759	1.00	13.38	C
ATOM	1187	O ASP A 147	9.921	48.691	11.764	1.00	16.42	O
ATOM	1188	CB ASP A 147	7.215	47.753	12.412	1.00	19.10	C
ATOM	1189	CG ASP A 147	6.612	48.811	11.618	1.00	22.88	C
ATOM	1190	OD1 ASP A 147	6.596	49.992	12.051	1.00	26.77	O
ATOM	1191	OD2 ASP A 147	6.089	48.525	10.492	1.00	31.82	O
ATOM	1192	N SER A 148	9.730	50.234	13.437	1.00	11.24	N
ATOM	1193	CA SER A 148	10.865	51.085	13.035	1.00	11.41	C
ATOM	1194	C SER A 148	12.139	50.555	13.722	1.00	12.41	C
ATOM	1195	O SER A 148	13.221	51.082	13.532	1.00	11.93	O

FIGURE 4T

ATOM	1196	CB	SER A 148	10.616	52.571	13.462	1.00	13.47	C
ATOM	1197	OG	SER A 148	9.510	53.075	12.756	1.00	18.49	O
ATOM	1198	N	ILE A 149	12.012	49.565	14.603	1.00	10.17	N
ATOM	1199	CA	ILE A 149	13.138	49.082	15.390	1.00	9.25	C
ATOM	1200	C	ILE A 149	13.560	47.734	14.780	1.00	11.79	C
ATOM	1201	O	ILE A 149	12.711	46.816	14.679	1.00	13.50	O
ATOM	1202	CB	ILE A 149	12.719	48.879	16.846	1.00	10.26	C
ATOM	1203	CG1	ILE A 149	12.195	50.215	17.445	1.00	11.46	C
ATOM	1204	CD1	ILE A 149	13.149	51.331	17.249	1.00	13.52	C
ATOM	1205	CG2	ILE A 149	13.915	48.281	17.639	1.00	13.68	C
ATOM	1206	N	LEU A 150	14.836	47.618	14.366	1.00	11.05	N
ATOM	1207	CA	LEU A 150	15.293	46.371	13.706	1.00	10.73	C
ATOM	1208	C	LEU A 150	16.269	45.659	14.615	1.00	12.50	C
ATOM	1209	O	LEU A 150	16.952	46.299	15.430	1.00	14.29	O
ATOM	1210	CB	LEU A 150	15.998	46.711	12.381	1.00	12.10	C
ATOM	1211	CG	LEU A 150	15.081	47.364	11.321	1.00	15.53	C
ATOM	1212	CD1	LEU A 150	15.794	47.476	9.917	1.00	18.62	C
ATOM	1213	CD2	LEU A 150	13.705	46.699	11.169	1.00	20.40	C
ATOM	1214	N	LEU A 151	16.378	44.341	14.472	1.00	15.80	N
ATOM	1215	CA	LEU A 151	17.277	43.604	15.345	1.00	17.22	C
ATOM	1216	C	LEU A 151	18.331	42.877	14.516	1.00	16.07	C
ATOM	1217	O	LEU A 151	18.090	42.515	13.339	1.00	15.72	O
ATOM	1218	CB	LEU A 151	16.466	42.574	16.094	1.00	17.53	C
ATOM	1219	CG	LEU A 151	15.249	43.116	16.847	1.00	20.60	C
ATOM	1220	CD1	LEU A 151	14.379	42.026	17.314	1.00	25.61	C
ATOM	1221	CD2	LEU A 151	15.701	43.953	18.018	1.00	24.59	C
ATOM	1222	N	THR A 152	19.484	42.690	15.106	1.00	17.59	N
ATOM	1223	CA	THR A 152	20.493	41.843	14.454	1.00	17.17	C
ATOM	1224	C	THR A 152	20.303	40.429	14.974	1.00	20.42	C
ATOM	1225	O	THR A 152	19.555	40.160	15.964	1.00	16.52	O
ATOM	1226	CB	THR A 152	21.894	42.310	14.703	1.00	19.53	C
ATOM	1227	OG1	THR A 152	22.208	42.106	16.082	1.00	19.31	O
ATOM	1228	CG2	THR A 152	22.071	43.851	14.412	1.00	19.23	C
ATOM	1229	N	LEU A 153	20.975	39.485	14.309	1.00	19.93	N
ATOM	1230	CA	LEU A 153	20.793	38.079	14.714	1.00	21.52	C
ATOM	1231	C	LEU A 153	21.415	37.852	16.058	1.00	20.48	C
ATOM	1232	O	LEU A 153	20.977	36.943	16.790	1.00	21.14	O
ATOM	1233	CB	LEU A 153	21.396	37.131	13.692	1.00	21.93	C
ATOM	1234	CG	LEU A 153	20.468	36.957	12.485	1.00	24.45	C
ATOM	1235	CD1	LEU A 153	21.186	36.112	11.443	1.00	29.58	C
ATOM	1236	CD2	LEU A 153	19.117	36.317	12.829	1.00	24.29	C
ATOM	1237	N	ASP A 154	22.412	38.675	16.396	1.00	19.37	N
ATOM	1238	CA	ASP A 154	23.048	38.628	17.718	1.00	21.62	C
ATOM	1239	C	ASP A 154	22.385	39.509	18.792	1.00	18.86	C
ATOM	1240	O	ASP A 154	22.952	39.650	19.892	1.00	21.52	O
ATOM	1241	CB	ASP A 154	24.583	38.906	17.631	1.00	22.62	C
ATOM	1242	CG	ASP A 154	24.926	40.377	17.296	1.00	32.83	C
ATOM	1243	OD1	ASP A 154	25.986	40.911	17.778	1.00	38.47	O
ATOM	1244	OD2	ASP A 154	24.214	41.088	16.564	1.00	35.75	O
ATOM	1245	N	GLY A 155	21.209	40.090	18.478	1.00	16.18	N
ATOM	1246	CA	GLY A 155	20.380	40.763	19.476	1.00	15.22	C
ATOM	1247	C	GLY A 155	20.655	42.244	19.696	1.00	16.46	C
ATOM	1248	O	GLY A 155	20.243	42.842	20.700	1.00	18.18	O
ATOM	1249	N	ARG A 156	21.344	42.877	18.749	1.00	15.57	N
ATOM	1250	CA	ARG A 156	21.566	44.314	18.820	1.00	17.47	C
ATOM	1251	C	ARG A 156	20.297	44.970	18.258	1.00	14.35	C
ATOM	1252	O	ARG A 156	19.590	44.398	17.416	1.00	14.49	O
ATOM	1253	CB	ARG A 156	22.775	44.689	17.962	1.00	19.38	C
ATOM	1254	CG	ARG A 156	24.161	44.410	18.598	1.00	28.07	C
ATOM	1255	CD	ARG A 156	25.331	44.576	17.563	1.00	34.94	C

FIGURE 4U

ATOM	1256	NE	ARG A 156	25.271	43.561	16.486	1.00	41.05	N
ATOM	1257	CZ	ARG A 156	25.484	43.749	15.168	1.00	40.30	C
ATOM	1258	NH1	ARG A 156	25.800	44.943	14.642	1.00	41.17	N
ATOM	1259	NH2	ARG A 156	25.380	42.702	14.354	1.00	39.14	N
ATOM	1260	N	VAL A 157	19.989	46.128	18.772	1.00	12.09	N
ATOM	1261	CA	VAL A 157	18.725	46.802	18.485	1.00	11.18	C
ATOM	1262	C	VAL A 157	19.082	48.102	17.817	1.00	10.05	C
ATOM	1263	O	VAL A 157	19.878	48.875	18.346	1.00	11.59	O
ATOM	1264	CB	VAL A 157	17.986	47.123	19.838	1.00	10.36	C
ATOM	1265	CG1	VAL A 157	16.763	47.987	19.636	1.00	10.99	C
ATOM	1266	CG2	VAL A 157	17.595	45.790	20.526	1.00	12.24	C
ATOM	1267	N	LYS A 158	18.495	48.329	16.649	1.00	10.46	N
ATOM	1268	CA	LYS A 158	18.775	49.561	15.909	1.00	8.94	C
ATOM	1269	C	LYS A 158	17.541	50.239	15.375	1.00	10.28	C
ATOM	1270	O	LYS A 158	16.556	49.584	14.977	1.00	12.90	O
ATOM	1271	CB	LYS A 158	19.704	49.254	14.726	1.00	9.69	C
ATOM	1272	CG	LYS A 158	20.985	48.537	15.164	1.00	9.09	C
ATOM	1273	CD	LYS A 158	22.092	48.703	14.091	1.00	10.47	C
ATOM	1274	CE	LYS A 158	23.305	47.829	14.454	1.00	15.71	C
ATOM	1275	NZ	LYS A 158	24.582	48.494	13.909	1.00	18.73	N
ATOM	1276	N	LEU A 159	17.622	51.551	15.275	1.00	9.03	N
ATOM	1277	CA	LEU A 159	16.517	52.374	14.804	1.00	8.17	C
ATOM	1278	C	LEU A 159	16.645	52.553	13.294	1.00	9.55	C
ATOM	1279	O	LEU A 159	17.750	52.820	12.780	1.00	11.01	O
ATOM	1280	CB	LEU A 159	16.633	53.720	15.496	1.00	10.45	C
ATOM	1281	CG	LEU A 159	15.619	54.779	15.080	1.00	11.72	C
ATOM	1282	CD1	LEU A 159	14.156	54.252	15.329	1.00	12.28	C
ATOM	1283	CD2	LEU A 159	15.913	56.012	15.969	1.00	15.76	C
ATOM	1284	N	SER A 160	15.551	52.390	12.578	1.00	8.93	N
ATOM	1285	CA	SER A 160	15.548	52.553	11.140	1.00	10.21	C
ATOM	1286	C	SER A 160	14.340	53.386	10.700	1.00	11.85	C
ATOM	1287	O	SER A 160	13.665	54.015	11.521	1.00	9.82	O
ATOM	1288	CB	BSER A 160	15.490	51.174	10.517	0.35	11.55	C
ATOM	1289	CB	ASER A 160	15.598	51.211	10.458	0.65	12.05	C
ATOM	1290	OG	BSER A 160	14.241	50.573	10.792	0.35	13.78	O
ATOM	1291	OG	ASER A 160	15.958	51.397	9.093	0.65	13.60	O
ATOM	1292	N	ASP A 161	14.044	53.363	9.406	1.00	13.47	N
ATOM	1293	CA	ASP A 161	12.812	53.983	8.829	1.00	13.87	C
ATOM	1294	C	ASP A 161	12.770	55.502	9.096	1.00	11.99	C
ATOM	1295	O	ASP A 161	11.822	56.039	9.709	1.00	12.87	O
ATOM	1296	CB	ASP A 161	11.525	53.321	9.298	1.00	16.18	C
ATOM	1297	CG	ASP A 161	11.345	51.900	8.704	1.00	26.14	C
ATOM	1298	OD1	ASP A 161	12.145	51.465	7.812	1.00	29.71	O
ATOM	1299	OD2	ASP A 161	10.423	51.153	9.067	1.00	29.86	O
ATOM	1300	N	PHE A 162	13.776	56.172	8.563	1.00	11.14	N
ATOM	1301	CA	PHE A 162	13.920	57.621	8.705	1.00	12.81	C
ATOM	1302	C	PHE A 162	13.202	58.454	7.645	1.00	12.24	C
ATOM	1303	O	PHE A 162	13.478	59.682	7.528	1.00	13.50	O
ATOM	1304	CB	PHE A 162	15.418	57.974	8.697	1.00	11.97	C
ATOM	1305	CG	PHE A 162	16.090	57.699	10.010	1.00	9.54	C
ATOM	1306	CD1	PHE A 162	16.457	56.387	10.399	1.00	13.00	C
ATOM	1307	CE1	PHE A 162	17.033	56.175	11.646	1.00	13.37	C
ATOM	1308	CZ	PHE A 162	17.290	57.265	12.483	1.00	12.40	C
ATOM	1309	CE2	PHE A 162	16.960	58.559	12.084	1.00	12.30	C
ATOM	1310	CD2	PHE A 162	16.352	58.751	10.863	1.00	11.27	C
ATOM	1311	N	GLY A 163	12.268	57.858	6.906	1.00	13.82	N
ATOM	1312	CA	GLY A 163	11.562	58.634	5.886	1.00	13.48	C
ATOM	1313	C	GLY A 163	10.914	59.976	6.279	1.00	14.52	C
ATOM	1314	O	GLY A 163	10.907	60.975	5.505	1.00	14.41	O
ATOM	1315	N	PHE A 164	10.450	60.062	7.525	1.00	11.20	N

FIGURE 4V

ATOM	1316	CA	PHE	A	164	9.780	61.271	7.982	1.00	11.22	C
ATOM	1317	C	PHE	A	164	10.683	62.157	8.793	1.00	10.65	C
ATOM	1318	O	PHE	A	164	10.212	63.129	9.418	1.00	10.34	O
ATOM	1319	CB	BPHE	A	164	8.500	60.911	8.742	0.35	13.03	C
ATOM	1320	CB	APHE	A	164	8.604	60.908	8.893	0.65	13.79	C
ATOM	1321	CG	BPHE	A	164	7.525	60.088	7.925	0.35	15.59	C
ATOM	1322	CG	APHE	A	164	7.327	60.560	8.168	0.65	18.35	C
ATOM	1323	CD1	BPHE	A	164	7.727	58.744	7.727	0.35	17.23	C
ATOM	1324	CD1	APHE	A	164	6.498	59.550	8.676	0.65	20.64	C
ATOM	1325	CE1	BPHE	A	164	6.836	57.979	6.959	0.35	21.72	C
ATOM	1326	CE1	APHE	A	164	5.294	59.220	8.035	0.65	19.69	C
ATOM	1327	CZ	BPHE	A	164	5.720	58.586	6.414	0.35	20.85	C
ATOM	1328	CZ	APHE	A	164	4.913	59.926	6.883	0.65	22.80	C
ATOM	1329	CE2	BPHE	A	164	5.513	59.941	6.601	0.35	22.03	C
ATOM	1330	CE2	APHE	A	164	5.734	60.956	6.369	0.65	21.66	C
ATOM	1331	CD2	BPHE	A	164	6.415	60.684	7.360	0.35	20.62	C
ATOM	1332	CD2	APHE	A	164	6.928	61.270	7.032	0.65	19.72	C
ATOM	1333	N	CYS	A	165	11.975	61.890	8.785	1.00	8.33	N
ATOM	1334	CA	CYS	A	165	12.866	62.678	9.630	1.00	9.67	C
ATOM	1335	C	CYS	A	165	12.967	64.172	9.233	1.00	10.06	C
ATOM	1336	O	CYS	A	165	12.650	64.604	8.088	1.00	12.24	O
ATOM	1337	CB	CYS	A	165	14.239	62.035	9.812	1.00	11.17	C
ATOM	1338	SG	CYS	A	165	15.293	62.189	8.305	1.00	18.40	S
ATOM	1339	N	ALA	A	166	13.356	64.969	10.216	1.00	9.90	N
ATOM	1340	CA	ALA	A	166	13.475	66.394	10.046	1.00	10.42	C
ATOM	1341	C	ALA	A	166	14.739	66.869	10.760	1.00	10.54	C
ATOM	1342	O	ALA	A	166	15.224	66.284	11.739	1.00	11.08	O
ATOM	1343	CB	ALA	A	166	12.255	67.104	10.634	1.00	11.37	C
ATOM	1344	N	GLN	A	167	15.306	67.982	10.287	1.00	10.67	N
ATOM	1345	CA	GLN	A	167	16.433	68.619	10.935	1.00	10.61	C
ATOM	1346	C	GLN	A	167	15.999	69.985	11.425	1.00	12.37	C
ATOM	1347	O	GLN	A	167	15.420	70.753	10.646	1.00	14.92	O
ATOM	1348	CB	GLN	A	167	17.530	68.781	9.858	1.00	12.26	C
ATOM	1349	CG	GLN	A	167	18.713	69.623	10.280	1.00	15.60	C
ATOM	1350	CD	GLN	A	167	19.639	68.829	11.143	1.00	16.62	C
ATOM	1351	OE1	GLN	A	167	20.257	67.884	10.684	1.00	17.28	O
ATOM	1352	NE2	GLN	A	167	19.755	69.221	12.414	1.00	16.73	N
ATOM	1353	N	ILE	A	168	16.219	70.249	12.708	1.00	12.92	N
ATOM	1354	CA	ILE	A	168	16.024	71.589	13.227	1.00	13.79	C
ATOM	1355	C	ILE	A	168	17.375	72.263	13.355	1.00	16.40	C
ATOM	1356	O	ILE	A	168	18.438	71.614	13.445	1.00	15.31	O
ATOM	1357	CB	ILE	A	168	15.209	71.585	14.532	1.00	13.24	C
ATOM	1358	CG1	ILE	A	168	15.791	70.618	15.546	1.00	14.21	C
ATOM	1359	CD1	ILE	A	168	15.077	70.736	16.948	1.00	17.92	C
ATOM	1360	CG2	ILE	A	168	13.697	71.218	14.214	1.00	13.15	C
ATOM	1361	N	SER	A	169	17.327	73.586	13.370	1.00	18.92	N
ATOM	1362	CA	SER	A	169	18.548	74.385	13.425	1.00	22.30	C
ATOM	1363	C	SER	A	169	18.246	75.682	14.139	1.00	23.37	C
ATOM	1364	O	SER	A	169	17.103	75.970	14.467	1.00	20.18	O
ATOM	1365	CB	SER	A	169	19.014	74.719	12.004	1.00	22.79	C
ATOM	1366	OG	SER	A	169	18.036	75.434	11.277	1.00	26.18	O
ATOM	1367	N	LYS	A	170	19.273	76.504	14.325	1.00	27.15	N
ATOM	1368	CA	LYS	A	170	19.067	77.843	14.872	1.00	28.37	C
ATOM	1369	C	LYS	A	170	18.067	78.643	14.063	1.00	27.91	C
ATOM	1370	O	LYS	A	170	17.196	79.304	14.624	1.00	30.83	O
ATOM	1371	CB	LYS	A	170	20.426	78.586	14.946	1.00	30.13	C
ATOM	1372	N	ASP	A	171	18.186	78.570	12.750	1.00	29.61	N
ATOM	1373	CA	ASP	A	171	17.294	79.248	11.824	1.00	29.87	C
ATOM	1374	C	ASP	A	171	15.867	78.703	11.844	1.00	29.80	C
ATOM	1375	O	ASP	A	171	14.921	79.481	11.725	1.00	31.39	O

FIGURE 4W

ATOM	1376	CB	ASP	A	171	17.843	79.106	10.402	1.00	31.35	C
ATOM	1377	N	VAL	A	172	15.714	77.369	11.925	1.00	26.96	N
ATOM	1378	CA	VAL	A	172	14.390	76.723	11.880	1.00	24.06	C
ATOM	1379	C	VAL	A	172	14.296	75.794	13.083	1.00	20.12	C
ATOM	1380	O	VAL	A	172	14.585	74.593	12.984	1.00	17.74	O
ATOM	1381	CB	VAL	A	172	14.154	75.913	10.566	1.00	25.93	C
ATOM	1382	CG1	VAL	A	172	12.640	75.460	10.458	1.00	25.55	C
ATOM	1383	CG2	VAL	A	172	14.515	76.750	9.362	1.00	29.52	C
ATOM	1384	N	PRO	A	173	14.066	76.362	14.261	1.00	18.09	N
ATOM	1385	CA	PRO	A	173	14.181	75.598	15.493	1.00	17.54	C
ATOM	1386	C	PRO	A	173	12.990	74.665	15.758	1.00	14.47	C
ATOM	1387	O	PRO	A	173	13.180	73.829	16.605	1.00	15.92	O
ATOM	1388	CB	PRO	A	173	14.269	76.675	16.579	1.00	19.22	C
ATOM	1389	CG	PRO	A	173	13.518	77.888	15.942	1.00	19.62	C
ATOM	1390	CD	PRO	A	173	13.759	77.796	14.497	1.00	19.89	C
ATOM	1391	N	LYS	A	174	11.867	74.817	15.058	1.00	14.35	N
ATOM	1392	CA	LYS	A	174	10.699	73.955	15.280	1.00	12.12	C
ATOM	1393	C	LYS	A	174	10.114	73.498	13.968	1.00	12.33	C
ATOM	1394	O	LYS	A	174	10.252	74.167	12.915	1.00	12.75	O
ATOM	1395	CB	LYS	A	174	9.563	74.712	15.999	1.00	13.82	C
ATOM	1396	CG	LYS	A	174	9.946	75.391	17.333	1.00	17.26	C
ATOM	1397	CD	LYS	A	174	10.276	74.464	18.416	1.00	20.49	C
ATOM	1398	CE	LYS	A	174	10.242	75.226	19.782	1.00	25.33	C
ATOM	1399	NZ	LYS	A	174	11.027	74.503	20.812	1.00	26.71	N
ATOM	1400	N	ARG	A	175	9.402	72.384	14.024	1.00	9.90	N
ATOM	1401	CA	ARG	A	175	8.638	71.866	12.897	1.00	10.64	C
ATOM	1402	C	ARG	A	175	7.155	71.976	13.173	1.00	10.65	C
ATOM	1403	O	ARG	A	175	6.773	72.127	14.331	1.00	11.69	O
ATOM	1404	CB	ARG	A	175	8.963	70.374	12.637	1.00	12.01	C
ATOM	1405	CG	ARG	A	175	10.428	70.150	12.432	1.00	13.49	C
ATOM	1406	CD	ARG	A	175	10.997	71.052	11.387	1.00	15.35	C
ATOM	1407	NE	ARG	A	175	10.506	70.619	10.116	1.00	17.56	N
ATOM	1408	CZ	ARG	A	175	11.334	70.479	9.083	1.00	25.77	C
ATOM	1409	NH1	ARG	A	175	12.632	70.792	9.219	1.00	22.31	N
ATOM	1410	NH2	ARG	A	175	10.877	70.023	7.920	1.00	28.34	N
ATOM	1411	N	LYS	A	176	6.310	71.884	12.169	1.00	12.76	N
ATOM	1412	CA	LYS	A	176	4.858	71.816	12.468	1.00	13.73	C
ATOM	1413	C	LYS	A	176	4.065	70.870	11.598	1.00	13.58	C
ATOM	1414	O	LYS	A	176	2.856	70.857	11.655	1.00	15.23	O
ATOM	1415	CB	LYS	A	176	4.243	73.225	12.501	1.00	16.85	C
ATOM	1416	CG	LYS	A	176	4.644	74.081	11.285	1.00	18.27	C
ATOM	1417	CD	LYS	A	176	3.863	73.661	10.072	1.00	20.51	C
ATOM	1418	CE	LYS	A	176	3.809	74.737	8.964	1.00	26.84	C
ATOM	1419	NZ	LYS	A	176	5.183	75.121	8.479	1.00	28.43	N
HETATM	1420	N	SEP	A	177	4.768	70.055	10.829	1.00	13.46	N
HETATM	1421	CA	SEP	A	177	4.093	69.134	9.911	1.00	12.36	C
HETATM	1422	C	SEP	A	177	3.394	68.000	10.637	1.00	10.53	C
HETATM	1423	O	SEP	A	177	3.900	67.449	11.622	1.00	12.66	O
HETATM	1424	CB	SEP	A	177	5.133	68.493	8.981	1.00	12.77	C
HETATM	1425	OG	SEP	A	177	5.777	69.492	8.215	1.00	14.27	O
HETATM	1426	P	SEP	A	177	7.356	69.618	8.231	1.00	14.99	P
HETATM	1427	O1P	SEP	A	177	7.859	69.822	9.699	1.00	17.47	O
HETATM	1428	O2P	SEP	A	177	7.643	70.963	7.445	1.00	17.05	O
HETATM	1429	O3P	SEP	A	177	7.935	68.362	7.575	1.00	17.97	O
ATOM	1430	N	LEU	A	178	2.202	67.631	10.130	1.00	12.36	N
ATOM	1431	CA	LEU	A	178	1.495	66.482	10.676	1.00	14.50	C
ATOM	1432	C	LEU	A	178	2.041	65.211	10.012	1.00	13.90	C
ATOM	1433	O	LEU	A	178	1.641	64.851	8.867	1.00	16.12	O
ATOM	1434	CB	LEU	A	178	-0.018	66.630	10.306	1.00	17.41	C
ATOM	1435	CG	LEU	A	178	-0.809	65.417	10.783	1.00	20.12	C

FIGURE 4X

ATOM	1436	CD1	LEU A 178	-1.316	65.733	12.099	1.00	20.93	C
ATOM	1437	CD2	LEU A 178	-2.009	65.146	9.821	1.00	30.24	C
ATOM	1438	N	VAL A 179	2.947	64.536	10.682	1.00	13.68	N
ATOM	1439	CA	VAL A 179	3.626	63.371	10.107	1.00	14.09	C
ATOM	1440	C	VAL A 179	3.719	62.319	11.185	1.00	13.92	C
ATOM	1441	O	VAL A 179	3.763	62.617	12.406	1.00	15.95	O
ATOM	1442	CB	VAL A 179	5.072	63.680	9.576	1.00	14.27	C
ATOM	1443	CG1	VAL A 179	5.002	64.657	8.365	1.00	17.80	C
ATOM	1444	CG2	VAL A 179	5.918	64.247	10.641	1.00	20.28	C
ATOM	1445	N	GLY A 180	3.798	61.108	10.751	1.00	13.90	N
ATOM	1446	CA	GLY A 180	4.037	59.989	11.656	1.00	13.36	C
ATOM	1447	C	GLY A 180	2.948	58.972	11.417	1.00	12.77	C
ATOM	1448	O	GLY A 180	2.307	58.979	10.372	1.00	16.01	O
ATOM	1449	N	THR A 181	2.751	58.106	12.366	1.00	10.12	N
ATOM	1450	CA	THR A 181	1.726	57.057	12.259	1.00	10.40	C
ATOM	1451	C	THR A 181	0.710	57.328	13.371	1.00	12.80	C
ATOM	1452	O	THR A 181	1.116	57.466	14.533	1.00	12.95	O
ATOM	1453	CB	THR A 181	2.415	55.700	12.430	1.00	13.12	C
ATOM	1454	OG1	THR A 181	3.451	55.559	11.424	1.00	14.51	O
ATOM	1455	CG2	THR A 181	1.406	54.555	12.136	1.00	15.33	C
ATOM	1456	N	PRO A 182	-0.579	57.373	13.066	1.00	12.66	N
ATOM	1457	CA	PRO A 182	-1.625	57.908	13.983	1.00	12.21	C
ATOM	1458	C	PRO A 182	-1.511	57.516	15.470	1.00	11.56	C
ATOM	1459	O	PRO A 182	-1.463	58.447	16.339	1.00	13.00	O
ATOM	1460	CB	PRO A 182	-2.915	57.372	13.373	1.00	14.40	C
ATOM	1461	CG	PRO A 182	-2.630	57.402	11.925	1.00	16.21	C
ATOM	1462	CD	PRO A 182	-1.151	57.026	11.745	1.00	13.73	C
ATOM	1463	N	TYR A 183	-1.383	56.222	15.780	1.00	10.05	N
ATOM	1464	CA	TYR A 183	-1.501	55.776	17.159	1.00	8.90	C
ATOM	1465	C	TYR A 183	-0.267	56.140	17.986	1.00	8.87	C
ATOM	1466	O	TYR A 183	-0.298	56.072	19.224	1.00	10.15	O
ATOM	1467	CB	TYR A 183	-1.670	54.225	17.172	1.00	8.81	C
ATOM	1468	CG	TYR A 183	-2.869	53.781	16.382	1.00	10.55	C
ATOM	1469	CD1	TYR A 183	-2.756	53.443	15.049	1.00	9.81	C
ATOM	1470	CE1	TYR A 183	-3.889	53.035	14.322	1.00	12.57	C
ATOM	1471	CZ	TYR A 183	-5.121	53.009	14.941	1.00	12.40	C
ATOM	1472	OH	TYR A 183	-6.246	52.622	14.191	1.00	15.63	O
ATOM	1473	CE2	TYR A 183	-5.281	53.373	16.262	1.00	12.08	C
ATOM	1474	CD2	TYR A 183	-4.113	53.756	16.996	1.00	11.93	C
ATOM	1475	N	TRP A 184	0.837	56.458	17.275	1.00	6.24	N
ATOM	1476	CA	TRP A 184	2.090	56.829	17.956	1.00	7.39	C
ATOM	1477	C	TRP A 184	2.392	58.347	17.950	1.00	8.67	C
ATOM	1478	O	TRP A 184	3.374	58.779	18.568	1.00	9.65	O
ATOM	1479	CB	TRP A 184	3.280	56.128	17.264	1.00	8.46	C
ATOM	1480	CG	TRP A 184	3.297	54.633	17.534	1.00	7.98	C
ATOM	1481	CD1	TRP A 184	4.030	53.964	18.462	1.00	8.38	C
ATOM	1482	NE1	TRP A 184	3.783	52.608	18.370	1.00	9.41	N
ATOM	1483	CE2	TRP A 184	2.864	52.399	17.373	1.00	9.50	C
ATOM	1484	CD2	TRP A 184	2.553	53.641	16.816	1.00	8.81	C
ATOM	1485	CE3	TRP A 184	1.676	53.709	15.739	1.00	9.62	C
ATOM	1486	CZ3	TRP A 184	1.093	52.535	15.237	1.00	10.59	C
ATOM	1487	CH2	TRP A 184	1.415	51.298	15.830	1.00	11.10	C
ATOM	1488	CZ2	TRP A 184	2.304	51.191	16.876	1.00	11.66	C
ATOM	1489	N	MET A 185	1.526	59.136	17.329	1.00	8.01	N
ATOM	1490	CA	MET A 185	1.810	60.579	17.174	1.00	9.95	C
ATOM	1491	C	MET A 185	1.625	61.344	18.464	1.00	8.30	C
ATOM	1492	O	MET A 185	0.613	61.182	19.166	1.00	10.11	O
ATOM	1493	CB	MET A 185	0.876	61.175	16.152	1.00	12.15	C
ATOM	1494	CG	BMET A 185	0.943	60.409	14.831	0.35	11.68	C
ATOM	1495	CG	AMET A 185	1.268	61.002	14.785	0.65	15.46	C

FIGURE 4Y

ATOM	1496	SD	BMET A 185	-0.032	61.134	13.466	0.35	20.34	S
ATOM	1497	SD	AMET A 185	-0.256	61.705	13.867	0.65	22.73	S
ATOM	1498	CE	BMET A 185	0.204	62.883	13.794	0.35	9.05	C
ATOM	1499	CE	AMET A 185	0.294	61.114	12.365	0.65	16.07	C
ATOM	1500	N	ALA A 186	2.557	62.255	18.761	1.00	8.40	N
ATOM	1501	CA	ALA A 186	2.414	63.079	19.952	1.00	9.30	C
ATOM	1502	C	ALA A 186	1.256	64.078	19.779	1.00	8.17	C
ATOM	1503	O	ALA A 186	0.947	64.544	18.682	1.00	7.35	O
ATOM	1504	CB	ALA A 186	3.675	63.863	20.148	1.00	9.31	C
ATOM	1505	N	PRO A 187	0.592	64.484	20.874	1.00	8.10	N
ATOM	1506	CA	PRO A 187	-0.588	65.349	20.726	1.00	9.54	C
ATOM	1507	C	PRO A 187	-0.241	66.680	20.041	1.00	9.25	C
ATOM	1508	O	PRO A 187	-1.086	67.179	19.304	1.00	10.75	O
ATOM	1509	CB	PRO A 187	-1.026	65.620	22.167	1.00	11.10	C
ATOM	1510	CG	PRO A 187	-0.536	64.371	22.945	1.00	13.94	C
ATOM	1511	CD	PRO A 187	0.807	64.072	22.272	1.00	9.31	C
ATOM	1512	N	GLU A 188	0.941	67.211	20.293	1.00	9.24	N
ATOM	1513	CA	GLU A 188	1.294	68.506	19.641	1.00	10.61	C
ATOM	1514	C	GLU A 188	1.477	68.341	18.130	1.00	12.25	C
ATOM	1515	O	GLU A 188	1.294	69.293	17.375	1.00	12.90	O
ATOM	1516	CB	GLU A 188	2.555	69.132	20.286	1.00	13.06	C
ATOM	1517	CG	GLU A 188	3.839	68.304	20.205	1.00	12.22	C
ATOM	1518	CD	GLU A 188	4.096	67.358	21.408	1.00	11.62	C
ATOM	1519	OE1	GLU A 188	5.290	67.177	21.681	1.00	11.54	O
ATOM	1520	OE2	GLU A 188	3.121	66.834	22.072	1.00	11.85	O
ATOM	1521	N	VAL A 189	1.825	67.120	17.669	1.00	8.86	N
ATOM	1522	CA	VAL A 189	1.903	66.886	16.224	1.00	10.55	C
ATOM	1523	C	VAL A 189	0.486	66.872	15.669	1.00	11.89	C
ATOM	1524	O	VAL A 189	0.210	67.508	14.636	1.00	10.78	O
ATOM	1525	CB	VAL A 189	2.631	65.575	15.914	1.00	11.02	C
ATOM	1526	CG1	VAL A 189	2.590	65.316	14.340	1.00	10.85	C
ATOM	1527	CG2	VAL A 189	4.039	65.571	16.454	1.00	9.84	C
ATOM	1528	N	ILE A 190	-0.437	66.146	16.335	1.00	9.02	N
ATOM	1529	CA	ILE A 190	-1.785	66.062	15.839	1.00	10.82	C
ATOM	1530	C	ILE A 190	-2.406	67.463	15.753	1.00	11.52	C
ATOM	1531	O	ILE A 190	-3.169	67.757	14.795	1.00	14.37	O
ATOM	1532	CB	ILE A 190	-2.612	65.121	16.733	1.00	10.77	C
ATOM	1533	CG1	ILE A 190	-1.925	63.760	16.715	1.00	11.16	C
ATOM	1534	CD1	ILE A 190	-2.444	62.833	17.822	1.00	11.16	C
ATOM	1535	CG2	ILE A 190	-4.034	65.015	16.202	1.00	11.05	C
ATOM	1536	N	SER A 191	-2.108	68.304	16.740	1.00	12.67	N
ATOM	1537	CA	SER A 191	-2.681	69.658	16.733	1.00	14.48	C
ATOM	1538	C	SER A 191	-1.900	70.618	15.827	1.00	14.97	C
ATOM	1539	O	SER A 191	-2.289	71.807	15.758	1.00	18.65	O
ATOM	1540	CB	BSER A 191	-2.690	70.248	18.169	0.35	14.86	C
ATOM	1541	CB	ASER A 191	-2.783	70.227	18.133	0.65	14.93	C
ATOM	1542	OG	BSER A 191	-2.999	69.321	19.224	0.35	16.01	O
ATOM	1543	OG	ASER A 191	-1.509	70.338	18.716	0.65	13.70	O
ATOM	1544	N	ARG A 192	-0.875	70.140	15.106	1.00	14.86	N
ATOM	1545	CA	ARG A 192	0.000	70.970	14.240	1.00	15.75	C
ATOM	1546	C	ARG A 192	0.554	72.209	14.987	1.00	15.23	C
ATOM	1547	O	ARG A 192	0.705	73.299	14.404	1.00	16.66	O
ATOM	1548	CB	ARG A 192	-0.617	71.374	12.885	1.00	17.48	C
ATOM	1549	CG	ARG A 192	-1.253	70.199	12.020	1.00	19.20	C
ATOM	1550	CD	ARG A 192	-2.165	70.773	10.953	1.00	25.95	C
ATOM	1551	NE	ARG A 192	-2.832	69.726	10.172	1.00	30.81	N
ATOM	1552	CZ	ARG A 192	-2.295	69.195	9.093	1.00	33.77	C
ATOM	1553	NH1	ARG A 192	-1.100	69.625	8.692	1.00	33.90	N
ATOM	1554	NH2	ARG A 192	-2.937	68.246	8.413	1.00	32.60	N
ATOM	1555	N	SER A 193	0.908	72.011	16.253	1.00	12.70	N

FIGURE 4Z

ATOM	1556	CA	SER	A	193	1.608	73.060	17.010	1.00	11.95	C
ATOM	1557	C	SER	A	193	3.058	73.031	16.577	1.00	13.55	C
ATOM	1558	O	SER	A	193	3.546	71.964	16.073	1.00	15.54	O
ATOM	1559	CB	SER	A	193	1.546	72.726	18.499	1.00	12.38	C
ATOM	1560	OG	SER	A	193	0.166	72.811	18.882	1.00	17.59	O
ATOM	1561	N	LEU	A	194	3.808	74.090	16.843	1.00	10.60	N
ATOM	1562	CA	LEU	A	194	5.254	73.999	16.649	1.00	10.41	C
ATOM	1563	C	LEU	A	194	5.852	73.017	17.662	1.00	10.82	C
ATOM	1564	O	LEU	A	194	5.482	73.033	18.878	1.00	12.22	O
ATOM	1565	CB	LEU	A	194	5.891	75.399	16.885	1.00	12.36	C
ATOM	1566	CG	LEU	A	194	5.549	76.410	15.816	1.00	14.42	C
ATOM	1567	CD1	LEU	A	194	6.088	77.737	16.355	1.00	20.14	C
ATOM	1568	CD2	LEU	A	194	6.165	76.005	14.521	1.00	19.06	C
ATOM	1569	N	TYR	A	195	6.754	72.137	17.186	1.00	8.49	N
ATOM	1570	CA	TYR	A	195	7.335	71.127	18.066	1.00	8.06	C
ATOM	1571	C	TYR	A	195	8.789	70.865	17.686	1.00	9.49	C
ATOM	1572	O	TYR	A	195	9.226	71.219	16.604	1.00	9.62	O
ATOM	1573	CB	TYR	A	195	6.496	69.851	17.954	1.00	9.99	C
ATOM	1574	CG	TYR	A	195	6.439	69.226	16.575	1.00	8.56	C
ATOM	1575	CD1	TYR	A	195	7.506	68.446	16.117	1.00	8.82	C
ATOM	1576	CE1	TYR	A	195	7.478	67.846	14.864	1.00	8.39	C
ATOM	1577	CZ	TYR	A	195	6.349	67.973	14.098	1.00	9.22	C
ATOM	1578	OH	TYR	A	195	6.286	67.441	12.830	1.00	10.36	O
ATOM	1579	CE2	TYR	A	195	5.252	68.741	14.516	1.00	8.80	C
ATOM	1580	CD2	TYR	A	195	5.305	69.365	15.781	1.00	9.46	C
ATOM	1581	N	ALA	A	196	9.467	70.118	18.540	1.00	8.73	N
ATOM	1582	CA	ALA	A	196	10.877	69.779	18.282	1.00	10.77	C
ATOM	1583	C	ALA	A	196	11.087	68.305	18.697	1.00	10.06	C
ATOM	1584	O	ALA	A	196	10.212	67.437	18.471	1.00	9.50	O
ATOM	1585	CB	ALA	A	196	11.773	70.773	19.041	1.00	12.36	C
ATOM	1586	N	THR	A	197	12.222	67.986	19.283	1.00	8.93	N
ATOM	1587	CA	THR	A	197	12.563	66.559	19.470	1.00	9.00	C
ATOM	1588	C	THR	A	197	11.676	65.809	20.467	1.00	10.46	C
ATOM	1589	O	THR	A	197	11.662	64.564	20.484	1.00	10.59	O
ATOM	1590	CB	THR	A	197	14.028	66.418	19.925	1.00	9.46	C
ATOM	1591	OG1	THR	A	197	14.237	67.188	21.117	1.00	12.69	O
ATOM	1592	CG2	THR	A	197	15.023	66.986	18.862	1.00	8.91	C
ATOM	1593	N	GLU	A	198	10.938	66.562	21.293	1.00	7.99	N
ATOM	1594	CA	GLU	A	198	10.162	65.885	22.341	1.00	9.91	C
ATOM	1595	C	GLU	A	198	9.140	64.912	21.786	1.00	8.33	C
ATOM	1596	O	GLU	A	198	8.685	64.011	22.487	1.00	9.01	O
ATOM	1597	CB	GLU	A	198	9.350	66.930	23.163	1.00	12.21	C
ATOM	1598	CG	GLU	A	198	10.221	68.109	23.583	1.00	15.73	C
ATOM	1599	CD	GLU	A	198	10.301	69.287	22.577	1.00	23.04	C
ATOM	1600	OE1	GLU	A	198	9.772	69.231	21.453	1.00	17.65	O
ATOM	1601	OE2	GLU	A	198	10.849	70.356	22.938	1.00	29.80	O
ATOM	1602	N	VAL	A	199	8.750	65.113	20.525	1.00	7.21	N
ATOM	1603	CA	VAL	A	199	7.724	64.256	19.938	1.00	7.54	C
ATOM	1604	C	VAL	A	199	8.153	62.799	19.863	1.00	7.89	C
ATOM	1605	O	VAL	A	199	7.307	61.877	20.006	1.00	8.50	O
ATOM	1606	CB	VAL	A	199	7.235	64.739	18.557	1.00	9.96	C
ATOM	1607	CG1	VAL	A	199	6.752	66.173	18.685	1.00	9.62	C
ATOM	1608	CG2	VAL	A	199	8.312	64.649	17.497	1.00	9.29	C
ATOM	1609	N	ASP	A	200	9.449	62.555	19.707	1.00	6.38	N
ATOM	1610	CA	ASP	A	200	9.949	61.159	19.594	1.00	7.47	C
ATOM	1611	C	ASP	A	200	9.851	60.431	20.944	1.00	7.82	C
ATOM	1612	O	ASP	A	200	9.719	59.207	21.004	1.00	8.32	O
ATOM	1613	CB	ASP	A	200	11.422	61.185	19.158	1.00	7.45	C
ATOM	1614	CG	ASP	A	200	11.605	61.427	17.703	1.00	10.61	C
ATOM	1615	OD1	ASP	A	200	10.683	61.256	16.896	1.00	8.39	O

FIGURE 4AA

ATOM	1616	OD2	ASP	A	200	12.750	61.788	17.354	1.00	10.13	O
ATOM	1617	N	ILE	A	201	9.935	61.225	22.044	1.00	7.20	N
ATOM	1618	CA	ILE	A	201	9.844	60.594	23.379	1.00	7.27	C
ATOM	1619	C	ILE	A	201	8.417	60.163	23.660	1.00	7.11	C
ATOM	1620	O	ILE	A	201	8.220	59.096	24.264	1.00	8.53	O
ATOM	1621	CB	ILE	A	201	10.336	61.598	24.456	1.00	7.31	C
ATOM	1622	CG1	ILE	A	201	11.757	62.067	24.129	1.00	8.54	C
ATOM	1623	CD1	ILE	A	201	12.827	60.966	24.008	1.00	11.46	C
ATOM	1624	CG2	ILE	A	201	10.172	60.962	25.893	1.00	8.88	C
ATOM	1625	N	TRP	A	202	7.425	60.951	23.264	1.00	6.93	N
ATOM	1626	CA	TRP	A	202	6.076	60.466	23.359	1.00	7.32	C
ATOM	1627	C	TRP	A	202	5.890	59.195	22.558	1.00	7.61	C
ATOM	1628	O	TRP	A	202	5.305	58.225	23.065	1.00	7.77	O
ATOM	1629	CB	TRP	A	202	5.079	61.500	22.864	1.00	6.52	C
ATOM	1630	CG	TRP	A	202	3.658	61.070	22.870	1.00	5.59	C
ATOM	1631	CD1	TRP	A	202	3.056	60.258	21.933	1.00	6.84	C
ATOM	1632	NE1	TRP	A	202	1.729	60.066	22.257	1.00	7.09	N
ATOM	1633	CE2	TRP	A	202	1.447	60.732	23.434	1.00	6.34	C
ATOM	1634	CD2	TRP	A	202	2.656	61.366	23.850	1.00	6.26	C
ATOM	1635	CE3	TRP	A	202	2.654	62.133	25.026	1.00	7.25	C
ATOM	1636	CZ3	TRP	A	202	1.450	62.229	25.762	1.00	8.08	C
ATOM	1637	CH2	TRP	A	202	0.267	61.593	25.320	1.00	9.21	C
ATOM	1638	CZ2	TRP	A	202	0.250	60.828	24.161	1.00	8.26	C
ATOM	1639	N	SER	A	203	6.281	59.200	21.283	1.00	7.30	N
ATOM	1640	CA	SER	A	203	6.160	57.946	20.492	1.00	7.28	C
ATOM	1641	C	SER	A	203	6.842	56.739	21.159	1.00	7.85	C
ATOM	1642	O	SER	A	203	6.330	55.613	21.081	1.00	9.09	O
ATOM	1643	CB	SER	A	203	6.714	58.168	19.053	1.00	7.37	C
ATOM	1644	OG	SER	A	203	6.056	59.282	18.408	1.00	9.64	O
ATOM	1645	N	LEU	A	204	8.052	56.946	21.730	1.00	7.96	N
ATOM	1646	CA	LEU	A	204	8.717	55.891	22.493	1.00	8.23	C
ATOM	1647	C	LEU	A	204	7.842	55.396	23.629	1.00	8.98	C
ATOM	1648	O	LEU	A	204	7.795	54.201	23.849	1.00	8.44	O
ATOM	1649	CB	LEU	A	204	10.068	56.373	22.999	1.00	9.47	C
ATOM	1650	CG	LEU	A	204	10.816	55.346	23.843	1.00	13.16	C
ATOM	1651	CD1	LEU	A	204	11.183	54.166	22.978	1.00	17.38	C
ATOM	1652	CD2	LEU	A	204	12.094	56.037	24.311	1.00	15.16	C
ATOM	1653	N	GLY	A	205	7.174	56.329	24.321	1.00	7.32	N
ATOM	1654	CA	GLY	A	205	6.216	55.982	25.391	1.00	8.11	C
ATOM	1655	C	GLY	A	205	5.180	55.032	24.856	1.00	7.63	C
ATOM	1656	O	GLY	A	205	4.814	54.017	25.506	1.00	8.35	O
ATOM	1657	N	ILE	A	206	4.629	55.363	23.684	1.00	7.27	N
ATOM	1658	CA	ILE	A	206	3.592	54.496	23.125	1.00	7.01	C
ATOM	1659	C	ILE	A	206	4.196	53.128	22.743	1.00	9.17	C
ATOM	1660	O	ILE	A	206	3.529	52.093	22.908	1.00	9.38	O
ATOM	1661	CB	ILE	A	206	2.953	55.213	21.878	1.00	7.93	C
ATOM	1662	CG1	ILE	A	206	2.306	56.571	22.249	1.00	7.47	C
ATOM	1663	CD1	ILE	A	206	1.066	56.395	23.228	1.00	9.57	C
ATOM	1664	CG2	ILE	A	206	1.925	54.272	21.184	1.00	7.57	C
ATOM	1665	N	MET	A	207	5.441	53.111	22.250	1.00	9.43	N
ATOM	1666	CA	MET	A	207	6.096	51.837	22.012	1.00	9.82	C
ATOM	1667	C	MET	A	207	6.273	51.016	23.327	1.00	10.15	C
ATOM	1668	O	MET	A	207	6.208	49.786	23.291	1.00	11.22	O
ATOM	1669	CB	MET	A	207	7.480	52.052	21.331	1.00	11.50	C
ATOM	1670	CG	MET	A	207	7.916	50.733	20.640	1.00	14.03	C
ATOM	1671	SD	MET	A	207	9.430	51.012	19.685	1.00	20.41	S
ATOM	1672	CE	MET	A	207	10.638	50.841	21.038	1.00	21.65	C
ATOM	1673	N	VAL	A	208	6.568	51.677	24.459	1.00	8.04	N
ATOM	1674	CA	VAL	A	208	6.652	50.946	25.724	1.00	9.84	C
ATOM	1675	C	VAL	A	208	5.292	50.318	26.075	1.00	10.44	C

FIGURE 4BB

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ATOM   1676  O    VAL A 208      5.201  49.148  26.50
ATOM   1677  CB   VAL A 208      7.176  51.854  26.87
ATOM   1678  CG1  VAL A 208      7.049  51.124  28.26
ATOM   1679  CG2  VAL A 208      8.673  52.293  26.55
ATOM   1680  N    ILE A 209      4.242  51.047  25.79
ATOM   1681  CA   ILE A 209      2.884  50.469  25.94
ATOM   1682  C    ILE A 209      2.724  49.248  25.02
ATOM   1683  O    ILE A 209      2.197  48.203  25.44
ATOM   1684  CB   ILE A 209      1.758  51.511  25.73
ATOM   1685  CG1  ILE A 209      1.837  52.557  26.87
ATOM   1686  CD1  ILE A 209      0.700  53.644  26.79
ATOM   1687  CG2  ILE A 209      0.359  50.839  25.70
ATOM   1688  N    GLU A 210      3.182  49.332  23.78
ATOM   1689  CA   GLU A 210      3.134  48.140  22.90
ATOM   1690  C    GLU A 210      3.873  46.986  23.61
ATOM   1691  O    GLU A 210      3.386  45.849  23.54
ATOM   1692  CB   GLU A 210      3.859  48.338  21.53
ATOM   1693  CG   GLU A 210      3.315  49.377  20.59
ATOM   1694  CD   GLU A 210      4.099  49.329  19.26
ATOM   1695  OE1  GLU A 210      4.948  50.187  18.99
ATOM   1696  OE2  GLU A 210      3.983  48.338  18.49
ATOM   1697  N    MET A 211      5.054  47.222  24.16
ATOM   1698  CA   MET A 211      5.833  46.124  24.83
ATOM   1699  C    MET A 211      5.153  45.538  26.05
ATOM   1700  O    MET A 211      5.217  44.313  26.26
ATOM   1701  CB   MET A 211      7.260  46.559  25.14
ATOM   1702  CG   MET A 211      8.028  46.807  23.84
ATOM   1703  SD   MET A 211      9.789  47.110  24.16
ATOM   1704  CE   MET A 211      9.830  48.653  24.71
ATOM   1705  N    VAL A 212      4.458  46.380  26.81
ATOM   1706  CA   VAL A 212      3.802  45.870  28.01
ATOM   1707  C    VAL A 212      2.435  45.261  27.80
ATOM   1708  O    VAL A 212      2.124  44.192  28.34
ATOM   1709  CB   VAL A 212      3.682  46.981  29.05
ATOM   1710  CG1  VAL A 212      2.849  46.514  30.35
ATOM   1711  CG2  VAL A 212      5.090  47.467  29.45
ATOM   1712  N    ASP A 213      1.606  45.939  26.98
ATOM   1713  CA   ASP A 213      0.200  45.520  26.71
ATOM   1714  C    ASP A 213      0.026  44.676  25.45
ATOM   1715  O    ASP A 213     -0.984  43.937  25.3
ATOM   1716  CB   ASP A 213     -0.684  46.743  26.53
ATOM   1717  CG   ASP A 213     -1.027  47.438  27.81
ATOM   1718  OD1  ASP A 213     -0.830  46.904  29.0
ATOM   1719  OD2  ASP A 213     -1.575  48.563  27.8
ATOM   1720  N    GLY A 214      0.897  44.845  24.4
ATOM   1721  CA   GLY A 214      0.766  44.089  23.2
ATOM   1722  C    GLY A 214      0.292  44.914  22.0
ATOM   1723  O    GLY A 214      0.261  44.439  20.9
ATOM   1724  N    GLU A 215     -0.147  46.139  22.3
ATOM   1725  CA   GLU A 215     -0.659  47.020  21.2
ATOM   1726  C    GLU A 215     -0.679  48.439  21.7
ATOM   1727  O    GLU A 215     -0.697  48.635  23.0
ATOM   1728  CB   GLU A 215     -2.080  46.651  20.8
ATOM   1729  CG   GLU A 215     -3.122  46.691  21.8
ATOM   1730  CD   GLU A 215     -4.533  46.304  21.3
ATOM   1731  OE1  GLU A 215     -4.641  45.655  20.2
ATOM   1732  OE2  GLU A 215     -5.553  46.701  21.9
ATOM   1733  N    PRO A 216     -0.681  49.447  20.9
ATOM   1734  CA   PRO A 216     -0.789  50.816  21.4
ATOM   1735  C    PRO A 216     -2.197  51.123  21.9
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FIGURE 4CC

ATOM	1736	O	PRO	A	216	-3.182	50.457	21.634	1.00	11.41	O
ATOM	1737	CB	PRO	A	216	-0.544	51.723	20.253	1.00	12.59	C
ATOM	1738	CG	PRO	A	216	-0.513	50.870	19.094	1.00	14.60	C
ATOM	1739	CD	PRO	A	216	-0.539	49.406	19.479	1.00	12.29	C
ATOM	1740	N	PRO	A	217	-2.337	52.233	22.658	1.00	10.60	N
ATOM	1741	CA	PRO	A	217	-3.673	52.685	23.073	1.00	11.93	C
ATOM	1742	C	PRO	A	217	-4.580	53.004	21.869	1.00	11.30	C
ATOM	1743	O	PRO	A	217	-4.119	53.352	20.756	1.00	11.28	O
ATOM	1744	CB	PRO	A	217	-3.390	54.022	23.837	1.00	13.60	C
ATOM	1745	CG	PRO	A	217	-1.958	53.876	24.277	1.00	15.40	C
ATOM	1746	CD	PRO	A	217	-1.231	53.114	23.141	1.00	10.48	C
ATOM	1747	N	TYR	A	218	-5.894	52.796	22.055	1.00	11.15	N
ATOM	1748	CA	TYR	A	218	-6.905	53.135	21.082	1.00	12.23	C
ATOM	1749	C	TYR	A	218	-6.804	52.316	19.791	1.00	12.03	C
ATOM	1750	O	TYR	A	218	-7.333	52.743	18.781	1.00	12.64	O
ATOM	1751	CB	TYR	A	218	-6.822	54.624	20.732	1.00	13.61	C
ATOM	1752	CG	TYR	A	218	-6.842	55.509	21.959	1.00	13.73	C
ATOM	1753	CD1	TYR	A	218	-7.840	55.375	22.887	1.00	17.17	C
ATOM	1754	CE1	TYR	A	218	-7.859	56.235	24.042	1.00	18.06	C
ATOM	1755	CZ	TYR	A	218	-6.829	57.169	24.197	1.00	18.73	C
ATOM	1756	OH	TYR	A	218	-6.801	58.024	25.274	1.00	20.43	O
ATOM	1757	CE2	TYR	A	218	-5.840	57.304	23.270	1.00	15.71	C
ATOM	1758	CD2	TYR	A	218	-5.835	56.434	22.173	1.00	14.33	C
ATOM	1759	N	PHE	A	219	-6.181	51.146	19.861	1.00	11.61	N
ATOM	1760	CA	PHE	A	219	-5.855	50.413	18.648	1.00	14.29	C
ATOM	1761	C	PHE	A	219	-7.080	49.926	17.912	1.00	16.67	C
ATOM	1762	O	PHE	A	219	-7.023	49.781	16.678	1.00	18.51	O
ATOM	1763	CB	PHE	A	219	-4.897	49.234	18.940	1.00	14.89	C
ATOM	1764	CG	PHE	A	219	-3.923	48.968	17.851	1.00	15.21	C
ATOM	1765	CD1	PHE	A	219	-3.540	47.668	17.546	1.00	14.86	C
ATOM	1766	CE1	PHE	A	219	-2.621	47.440	16.553	1.00	14.73	C
ATOM	1767	CZ	PHE	A	219	-1.990	48.482	15.911	1.00	14.90	C
ATOM	1768	CE2	PHE	A	219	-2.331	49.783	16.210	1.00	14.90	C
ATOM	1769	CD2	PHE	A	219	-3.298	50.009	17.187	1.00	13.03	C
ATOM	1770	N	SER	A	220	-8.178	49.712	18.620	1.00	19.72	N
ATOM	1771	CA	SER	A	220	-9.410	49.245	17.961	1.00	22.26	C
ATOM	1772	C	SER	A	220	-10.215	50.413	17.394	1.00	22.26	C
ATOM	1773	O	SER	A	220	-11.208	50.210	16.683	1.00	23.48	O
ATOM	1774	CB	SER	A	220	-10.273	48.407	18.915	1.00	24.24	C
ATOM	1775	OG	SER	A	220	-10.626	49.183	20.064	1.00	27.24	O
ATOM	1776	N	ASP	A	221	-9.811	51.647	17.691	1.00	17.37	N
ATOM	1777	CA	ASP	A	221	-10.462	52.794	17.037	1.00	17.42	C
ATOM	1778	C	ASP	A	221	-9.913	52.942	15.645	1.00	15.64	C
ATOM	1779	O	ASP	A	221	-8.808	52.507	15.391	1.00	17.11	O
ATOM	1780	CB	ASP	A	221	-10.194	54.096	17.813	1.00	17.42	C
ATOM	1781	CG	ASP	A	221	-10.966	54.173	19.119	1.00	25.16	C
ATOM	1782	OD1	ASP	A	221	-12.123	53.726	19.111	1.00	31.16	O
ATOM	1783	OD2	ASP	A	221	-10.492	54.619	20.179	1.00	27.85	O
ATOM	1784	N	SER	A	222	-10.678	53.536	14.737	1.00	14.70	N
ATOM	1785	CA	SER	A	222	-10.139	53.953	13.424	1.00	15.25	C
ATOM	1786	C	SER	A	222	-8.944	54.901	13.676	1.00	13.87	C
ATOM	1787	O	SER	A	222	-8.849	55.534	14.728	1.00	13.38	O
ATOM	1788	CB	SER	A	222	-11.216	54.622	12.586	1.00	16.93	C
ATOM	1789	OG	SER	A	222	-11.267	56.040	12.861	1.00	22.00	O
ATOM	1790	N	PRO	A	223	-8.015	54.974	12.734	1.00	12.63	N
ATOM	1791	CA	PRO	A	223	-6.841	55.843	12.895	1.00	12.58	C
ATOM	1792	C	PRO	A	223	-7.257	57.313	13.122	1.00	13.79	C
ATOM	1793	O	PRO	A	223	-6.640	57.975	13.963	1.00	13.89	O
ATOM	1794	CB	PRO	A	223	-6.106	55.684	11.566	1.00	14.54	C
ATOM	1795	CG	PRO	A	223	-6.449	54.177	11.164	1.00	17.03	C

FIGURE 4DD

ATOM	1796	CD	PRO	A	223	-7.911	54.108	11.521	1.00	14.10	C
ATOM	1797	N	VAL	A	224	-8.286	57.795	12.428	1.00	14.16	N
ATOM	1798	CA	VAL	A	224	-8.719	59.185	12.580	1.00	16.18	C
ATOM	1799	C	VAL	A	224	-9.381	59.409	13.962	1.00	15.57	C
ATOM	1800	O	VAL	A	224	-9.080	60.397	14.658	1.00	15.46	O
ATOM	1801	CB	VAL	A	224	-9.673	59.535	11.421	1.00	18.99	C
ATOM	1802	CG1	VAL	A	224	-10.386	60.805	11.717	1.00	20.49	C
ATOM	1803	CG2	VAL	A	224	-8.851	59.691	10.102	1.00	22.12	C
ATOM	1804	N	GLN	A	225	-10.176	58.446	14.405	1.00	14.97	N
ATOM	1805	CA	GLN	A	225	-10.731	58.528	15.747	1.00	14.39	C
ATOM	1806	C	GLN	A	225	-9.634	58.444	16.830	1.00	13.92	C
ATOM	1807	O	GLN	A	225	-9.678	59.193	17.856	1.00	14.67	O
ATOM	1808	CB	BGLN	A	225	-11.794	57.439	15.930	0.35	14.65	C
ATOM	1809	CB	AGLN	A	225	-11.799	57.430	15.970	0.65	16.87	C
ATOM	1810	CG	BGLN	A	225	-13.004	57.707	15.058	0.35	13.93	C
ATOM	1811	CG	AGLN	A	225	-12.231	57.269	17.424	0.65	21.48	C
ATOM	1812	CD	AGLN	A	225	-13.050	58.438	18.029	0.65	30.11	C
ATOM	1813	OE1	AGLN	A	225	-13.163	59.528	17.457	0.65	33.96	O
ATOM	1814	NE2	AGLN	A	225	-13.635	58.180	19.194	0.65	32.00	N
ATOM	1815	N	ALA	A	226	-8.645	57.565	16.649	1.00	11.43	N
ATOM	1816	CA	ALA	A	226	-7.581	57.450	17.649	1.00	12.14	C
ATOM	1817	C	ALA	A	226	-6.872	58.822	17.785	1.00	10.16	C
ATOM	1818	O	ALA	A	226	-6.521	59.248	18.893	1.00	11.83	O
ATOM	1819	CB	ALA	A	226	-6.569	56.382	17.253	1.00	11.42	C
ATOM	1820	N	MET	A	227	-6.606	59.457	16.652	1.00	11.14	N
ATOM	1821	CA	MET	A	227	-5.918	60.768	16.662	1.00	11.08	C
ATOM	1822	C	MET	A	227	-6.714	61.816	17.424	1.00	11.05	C
ATOM	1823	O	MET	A	227	-6.107	62.626	18.140	1.00	11.22	O
ATOM	1824	CB	MET	A	227	-5.625	61.267	15.256	1.00	11.85	C
ATOM	1825	CG	BMET	A	227	-4.493	60.477	14.633	0.35	13.17	C
ATOM	1826	CG	AMET	A	227	-4.452	60.514	14.682	0.65	15.25	C
ATOM	1827	SD	BMET	A	227	-4.307	60.675	12.850	0.35	14.48	S
ATOM	1828	SD	AMET	A	227	-3.872	61.220	13.132	0.65	19.84	S
ATOM	1829	CE	BMET	A	227	-3.913	62.430	12.732	0.35	13.01	C
ATOM	1830	CE	AMET	A	227	-5.273	60.839	12.126	0.65	16.60	C
ATOM	1831	N	LYS	A	228	-8.026	61.789	17.261	1.00	11.40	N
ATOM	1832	CA	LYS	A	228	-8.908	62.734	17.968	1.00	14.20	C
ATOM	1833	C	LYS	A	228	-8.804	62.504	19.469	1.00	13.98	C
ATOM	1834	O	LYS	A	228	-8.724	63.488	20.289	1.00	14.07	O
ATOM	1835	CB	LYS	A	228	-10.356	62.534	17.547	1.00	15.01	C
ATOM	1836	CG	LYS	A	228	-10.672	63.121	16.194	1.00	23.56	C
ATOM	1837	CD	LYS	A	228	-12.169	62.928	15.932	1.00	31.05	C
ATOM	1838	CE	LYS	A	228	-12.501	62.919	14.412	1.00	37.91	C
ATOM	1839	NZ	LYS	A	228	-11.649	63.879	13.635	1.00	39.07	N
ATOM	1840	N	ARG	A	229	-8.737	61.236	19.888	1.00	11.77	N
ATOM	1841	CA	ARG	A	229	-8.620	60.969	21.312	1.00	12.30	C
ATOM	1842	C	ARG	A	229	-7.267	61.389	21.840	1.00	12.27	C
ATOM	1843	O	ARG	A	229	-7.155	62.000	22.916	1.00	12.33	O
ATOM	1844	CB	ARG	A	229	-8.843	59.472	21.646	1.00	14.60	C
ATOM	1845	CG	ARG	A	229	-10.256	59.046	21.239	1.00	20.61	C
ATOM	1846	CD	ARG	A	229	-10.672	57.695	21.668	1.00	30.02	C
ATOM	1847	NE	ARG	A	229	-10.840	57.579	23.113	1.00	35.51	N
ATOM	1848	CZ	ARG	A	229	-11.268	56.455	23.693	1.00	39.66	C
ATOM	1849	NH1	ARG	A	229	-11.374	56.378	25.006	1.00	39.35	N
ATOM	1850	NH2	ARG	A	229	-11.566	55.395	22.941	1.00	39.25	N
ATOM	1851	N	LEU	A	230	-6.223	61.073	21.074	1.00	9.56	N
ATOM	1852	CA	LEU	A	230	-4.879	61.401	21.545	1.00	10.70	C
ATOM	1853	C	LEU	A	230	-4.664	62.926	21.599	1.00	10.18	C
ATOM	1854	O	LEU	A	230	-3.944	63.417	22.492	1.00	12.43	O
ATOM	1855	CB	LEU	A	230	-3.818	60.854	20.584	1.00	9.90	C

FIGURE 4EE

ATOM	1856	CG	LEU A 230	-3.700	59.360	20.786	1.00	8.71	C
ATOM	1857	CD1	LEU A 230	-3.115	58.664	19.468	1.00	13.82	C
ATOM	1858	CD2	LEU A 230	-2.788	58.965	21.915	1.00	12.03	C
ATOM	1859	N	ARG A 231	-5.259	63.647	20.654	1.00	11.94	N
ATOM	1860	CA	ARG A 231	-5.050	65.088	20.521	1.00	13.39	C
ATOM	1861	C	ARG A 231	-5.458	65.785	21.784	1.00	14.05	C
ATOM	1862	O	ARG A 231	-4.724	66.643	22.260	1.00	18.09	O
ATOM	1863	CB	ARG A 231	-5.868	65.630	19.348	1.00	13.53	C
ATOM	1864	CG	ARG A 231	-5.621	67.141	18.964	1.00	16.48	C
ATOM	1865	CD	ARG A 231	-6.780	67.672	18.143	1.00	16.02	C
ATOM	1866	NE	ARG A 231	-6.457	68.999	17.556	1.00	22.48	N
ATOM	1867	CZ	ARG A 231	-6.444	70.144	18.220	1.00	23.29	C
ATOM	1868	NH1	ARG A 231	-6.718	70.187	19.510	1.00	23.31	N
ATOM	1869	NH2	ARG A 231	-6.161	71.257	17.567	1.00	24.81	N
ATOM	1870	N	ASP A 232	-6.580	65.387	22.341	1.00	14.93	N
ATOM	1871	CA	ASP A 232	-7.097	66.167	23.487	1.00	17.99	C
ATOM	1872	C	ASP A 232	-7.226	65.476	24.849	1.00	17.24	C
ATOM	1873	O	ASP A 232	-7.595	66.126	25.817	1.00	16.11	O
ATOM	1874	CB	ASP A 232	-8.414	66.819	23.135	1.00	21.42	C
ATOM	1875	CG	ASP A 232	-8.325	67.742	21.890	1.00	25.74	C
ATOM	1876	OD1	ASP A 232	-7.248	68.352	21.559	1.00	26.40	O
ATOM	1877	OD2	ASP A 232	-9.349	67.913	21.190	1.00	31.42	O
ATOM	1878	N	SER A 233	-6.905	64.203	24.949	1.00	12.98	N
ATOM	1879	CA	SER A 233	-7.146	63.470	26.202	1.00	13.02	C
ATOM	1880	C	SER A 233	-5.932	63.440	27.111	1.00	12.86	C
ATOM	1881	O	SER A 233	-4.797	63.494	26.658	1.00	11.91	O
ATOM	1882	CB	SER A 233	-7.605	62.017	25.899	1.00	14.97	C
ATOM	1883	OG	SER A 233	-8.783	62.036	25.136	1.00	17.32	O
ATOM	1884	N	PRO A 234	-6.097	63.262	28.420	1.00	11.22	N
ATOM	1885	CA	PRO A 234	-4.949	62.968	29.284	1.00	12.07	C
ATOM	1886	C	PRO A 234	-4.181	61.754	28.708	1.00	11.78	C
ATOM	1887	O	PRO A 234	-4.794	60.941	27.999	1.00	13.26	O
ATOM	1888	CB	PRO A 234	-5.582	62.614	30.632	1.00	13.85	C
ATOM	1889	CG	PRO A 234	-6.858	63.382	30.580	1.00	14.18	C
ATOM	1890	CD	PRO A 234	-7.379	63.296	29.171	1.00	14.29	C
ATOM	1891	N	PRO A 235	-2.909	61.620	29.031	1.00	12.43	N
ATOM	1892	CA	PRO A 235	-2.128	60.562	28.401	1.00	12.33	C
ATOM	1893	C	PRO A 235	-2.685	59.179	28.693	1.00	13.90	C
ATOM	1894	O	PRO A 235	-3.274	58.934	29.770	1.00	12.03	O
ATOM	1895	CB	PRO A 235	-0.744	60.690	29.025	1.00	15.49	C
ATOM	1896	CG	PRO A 235	-0.681	62.136	29.549	1.00	16.66	C
ATOM	1897	CD	PRO A 235	-2.107	62.396	30.007	1.00	11.62	C
ATOM	1898	N	PRO A 236	-2.485	58.266	27.751	1.00	12.06	N
ATOM	1899	CA	PRO A 236	-3.067	56.940	27.894	1.00	14.02	C
ATOM	1900	C	PRO A 236	-2.324	56.206	28.965	1.00	16.52	C
ATOM	1901	O	PRO A 236	-1.143	56.431	29.196	1.00	17.17	O
ATOM	1902	CB	PRO A 236	-2.815	56.305	26.510	1.00	13.82	C
ATOM	1903	CG	PRO A 236	-1.650	57.081	25.922	1.00	15.95	C
ATOM	1904	CD	PRO A 236	-1.748	58.464	26.490	1.00	13.01	C
ATOM	1905	N	LYS A 237	-3.048	55.300	29.604	1.00	20.86	N
ATOM	1906	CA	LYS A 237	-2.499	54.534	30.694	1.00	23.45	C
ATOM	1907	C	LYS A 237	-2.296	53.081	30.257	1.00	23.21	C
ATOM	1908	O	LYS A 237	-2.920	52.632	29.284	1.00	22.52	O
ATOM	1909	CB	LYS A 237	-3.471	54.644	31.865	1.00	25.76	C
ATOM	1910	CG	LYS A 237	-3.451	56.061	32.459	1.00	30.23	C
ATOM	1911	CD	LYS A 237	-3.831	56.105	33.950	1.00	37.37	C
ATOM	1912	CE	LYS A 237	-5.274	56.590	34.143	1.00	41.93	C
ATOM	1913	NZ	LYS A 237	-5.652	57.721	33.209	1.00	45.39	N
ATOM	1914	N	LEU A 238	-1.377	52.391	30.930	1.00	22.06	N
ATOM	1915	CA	LEU A 238	-1.179	50.966	30.681	1.00	21.36	C

FIGURE 4FF

ATOM	1916	C	LEU	A	238	-2.417	50.185	31.094	1.00	21.85	C
ATOM	1917	O	LEU	A	238	-2.928	50.409	32.178	1.00	24.44	O
ATOM	1918	CB	LEU	A	238	-0.072	50.434	31.576	1.00	21.93	C
ATOM	1919	CG	LEU	A	238	1.347	50.798	31.203	1.00	24.88	C
ATOM	1920	CD1	LEU	A	238	2.248	50.357	32.356	1.00	24.48	C
ATOM	1921	CD2	LEU	A	238	1.710	50.084	29.886	1.00	21.09	C
ATOM	1922	N	LYS	A	239	-2.847	49.258	30.266	1.00	20.82	N
ATOM	1923	CA	LYS	A	239	-3.870	48.282	30.679	1.00	22.77	C
ATOM	1924	C	LYS	A	239	-3.328	47.309	31.739	1.00	20.78	C
ATOM	1925	O	LYS	A	239	-3.987	47.045	32.750	1.00	21.34	O
ATOM	1926	CB	LYS	A	239	-4.384	47.543	29.488	1.00	21.61	C
ATOM	1927	CG	LYS	A	239	-5.167	48.489	28.511	1.00	27.26	C
ATOM	1928	CD	LYS	A	239	-5.415	47.860	27.167	1.00	32.53	C
ATOM	1929	CE	LYS	A	239	-6.495	48.640	26.409	1.00	37.38	C
ATOM	1930	NZ	LYS	A	239	-7.504	47.716	25.779	1.00	41.05	N
ATOM	1931	N	ASN	A	240	-2.106	46.829	31.541	1.00	19.71	N
ATOM	1932	CA	ASN	A	240	-1.502	45.911	32.483	1.00	16.51	C
ATOM	1933	C	ASN	A	240	-0.587	46.568	33.517	1.00	16.42	C
ATOM	1934	O	ASN	A	240	0.449	46.046	33.833	1.00	18.50	O
ATOM	1935	CB	ASN	A	240	-0.798	44.802	31.683	1.00	14.83	C
ATOM	1936	CG	ASN	A	240	-1.822	43.905	30.979	1.00	18.91	C
ATOM	1937	OD1	ASN	A	240	-2.307	42.942	31.542	1.00	19.99	O
ATOM	1938	ND2	ASN	A	240	-2.196	44.271	29.777	1.00	23.25	N
ATOM	1939	N	SER	A	241	-1.017	47.691	34.122	1.00	19.82	N
ATOM	1940	CA	SER	A	241	-0.186	48.374	35.139	1.00	22.36	C
ATOM	1941	C	SER	A	241	0.073	47.538	36.361	1.00	20.03	C
ATOM	1942	O	SER	A	241	1.092	47.715	37.038	1.00	22.16	O
ATOM	1943	CB	SER	A	241	-0.863	49.667	35.608	1.00	23.57	C
ATOM	1944	OG	SER	A	241	-2.195	49.387	35.952	1.00	30.32	O
ATOM	1945	N	HIS	A	242	-0.804	46.550	36.643	1.00	19.43	N
ATOM	1946	CA	HIS	A	242	-0.605	45.730	37.847	1.00	19.11	C
ATOM	1947	C	HIS	A	242	0.667	44.926	37.881	1.00	19.49	C
ATOM	1948	O	HIS	A	242	1.145	44.552	38.944	1.00	23.78	O
ATOM	1949	CB	HIS	A	242	-1.772	44.729	38.024	1.00	18.62	C
ATOM	1950	CG	HIS	A	242	-1.887	43.770	36.862	1.00	15.38	C
ATOM	1951	ND1	HIS	A	242	-1.310	42.510	36.850	1.00	20.24	N
ATOM	1952	CE1	HIS	A	242	-1.534	41.950	35.665	1.00	13.20	C
ATOM	1953	NE2	HIS	A	242	-2.175	42.813	34.906	1.00	17.21	N
ATOM	1954	CD2	HIS	A	242	-2.438	43.948	35.645	1.00	13.10	C
ATOM	1955	N	LYS	A	243	1.224	44.601	36.723	1.00	19.85	N
ATOM	1956	CA	LYS	A	243	2.413	43.766	36.763	1.00	21.56	C
ATOM	1957	C	LYS	A	243	3.695	44.535	36.475	1.00	19.39	C
ATOM	1958	O	LYS	A	243	4.716	43.931	36.310	1.00	23.08	O
ATOM	1959	CB	LYS	A	243	2.283	42.561	35.808	1.00	20.88	C
ATOM	1960	CG	LYS	A	243	1.946	42.924	34.424	1.00	24.29	C
ATOM	1961	CD	LYS	A	243	2.453	41.871	33.478	1.00	30.59	C
ATOM	1962	CE	LYS	A	243	1.534	41.804	32.314	1.00	28.80	C
ATOM	1963	NZ	LYS	A	243	1.938	40.724	31.322	1.00	28.74	N
ATOM	1964	N	VAL	A	244	3.621	45.850	36.380	1.00	19.41	N
ATOM	1965	CA	VAL	A	244	4.815	46.606	36.062	1.00	16.80	C
ATOM	1966	C	VAL	A	244	5.405	47.177	37.356	1.00	16.94	C
ATOM	1967	O	VAL	A	244	4.651	47.631	38.233	1.00	18.15	O
ATOM	1968	CB	VAL	A	244	4.421	47.738	35.131	1.00	18.29	C
ATOM	1969	CG1	VAL	A	244	5.628	48.612	34.818	1.00	21.72	C
ATOM	1970	CG2	VAL	A	244	3.836	47.180	33.795	1.00	20.06	C
ATOM	1971	N	SER	A	245	6.715	47.118	37.471	1.00	14.69	N
ATOM	1972	CA	SER	A	245	7.394	47.704	38.626	1.00	16.91	C
ATOM	1973	C	SER	A	245	7.158	49.203	38.760	1.00	17.10	C
ATOM	1974	O	SER	A	245	6.910	49.922	37.795	1.00	16.02	O
ATOM	1975	CB	SER	A	245	8.902	47.424	38.547	1.00	17.90	C

FIGURE 4GG

ATOM	1976	OG	SER	A	245	9.504	48.195	37.526	1.00 18.08	O
ATOM	1977	N	PRO	A	246	7.214	49.716	39.980	1.00 16.67	N
ATOM	1978	CA	PRO	A	246	7.118	51.173	40.200	1.00 14.64	C
ATOM	1979	C	PRO	A	246	8.177	51.918	39.359	1.00 14.70	C
ATOM	1980	O	PRO	A	246	7.887	53.005	38.871	1.00 14.51	O
ATOM	1981	CB	PRO	A	246	7.414	51.317	41.698	1.00 18.02	C
ATOM	1982	CG	PRO	A	246	6.915	49.965	42.235	1.00 17.89	C
ATOM	1983	CD	PRO	A	246	7.251	48.925	41.241	1.00 18.29	C
ATOM	1984	N	VAL	A	247	9.374	51.359	39.222	1.00 13.22	N
ATOM	1985	CA	VAL	A	247	10.449	52.099	38.503	1.00 12.85	C
ATOM	1986	C	VAL	A	247	10.093	52.161	37.011	1.00 12.42	C
ATOM	1987	O	VAL	A	247	10.277	53.224	36.388	1.00 12.80	O
ATOM	1988	CB	VAL	A	247	11.884	51.542	38.753	1.00 14.14	C
ATOM	1989	CG1	VAL	A	247	12.086	50.168	38.235	1.00 18.29	C
ATOM	1990	CG2	VAL	A	247	12.907	52.418	38.115	1.00 14.93	C
ATOM	1991	N	LEU	A	248	9.540	51.089	36.446	1.00 11.61	N
ATOM	1992	CA	LEU	A	248	9.150	51.184	35.025	1.00 13.31	C
ATOM	1993	C	LEU	A	248	7.915	52.081	34.843	1.00 12.97	C
ATOM	1994	O	LEU	A	248	7.802	52.839	33.871	1.00 12.11	O
ATOM	1995	CB	LEU	A	248	8.911	49.772	34.457	1.00 12.20	C
ATOM	1996	CG	LEU	A	248	8.326	49.685	33.021	1.00 13.80	C
ATOM	1997	CD1	LEU	A	248	9.131	50.550	32.019	1.00 14.35	C
ATOM	1998	CD2	LEU	A	248	8.267	48.234	32.581	1.00 14.42	C
ATOM	1999	N	ARG	A	249	6.974	52.039	35.773	1.00 11.52	N
ATOM	2000	CA	ARG	A	249	5.834	52.925	35.706	1.00 12.62	C
ATOM	2001	C	ARG	A	249	6.314	54.373	35.685	1.00 12.84	C
ATOM	2002	O	ARG	A	249	5.770	55.174	34.952	1.00 13.05	O
ATOM	2003	CB	BARG	A	249	4.964	52.696	36.939	0.25 12.33	C
ATOM	2004	CB	AARG	A	249	4.877	52.678	36.870	0.75 15.56	C
ATOM	2005	CG	BARG	A	249	3.797	53.646	37.109	0.25 9.14	C
ATOM	2006	CG	AARG	A	249	4.161	51.326	36.750	0.75 19.29	C
ATOM	2007	CD	BARG	A	249	2.893	53.302	38.312	0.25 13.35	C
ATOM	2008	CD	AARG	A	249	3.017	51.120	37.779	0.75 26.93	C
ATOM	2009	NE	BARG	A	249	3.043	51.901	38.740	0.25 16.87	N
ATOM	2010	NE	AARG	A	249	1.812	51.867	37.355	0.75 32.91	N
ATOM	2011	CZ	BARG	A	249	3.362	51.483	39.972	0.25 18.67	C
ATOM	2012	CZ	AARG	A	249	0.748	52.123	38.125	0.75 34.19	C
ATOM	2013	NH1	BARG	A	249	3.472	50.177	40.212	0.25 16.90	N
ATOM	2014	NH1	AARG	A	249	-0.279	52.803	37.638	0.75 34.31	N
ATOM	2015	NH2	BARG	A	249	3.594	52.347	40.961	0.25 18.61	N
ATOM	2016	NH2	AARG	A	249	0.725	51.729	39.392	0.75 36.84	N
ATOM	2017	N	ASP	A	250	7.312	54.701	36.518	1.00 12.28	N
ATOM	2018	CA	ASP	A	250	7.816	56.067	36.612	1.00 12.79	C
ATOM	2019	C	ASP	A	250	8.506	56.477	35.294	1.00 12.77	C
ATOM	2020	O	ASP	A	250	8.312	57.585	34.787	1.00 13.07	O
ATOM	2021	CB	ASP	A	250	8.836	56.190	37.717	1.00 14.77	C
ATOM	2022	CG	ASP	A	250	9.263	57.632	37.892	1.00 20.60	C
ATOM	2023	OD1	ASP	A	250	10.305	58.045	37.331	1.00 19.15	O
ATOM	2024	OD2	ASP	A	250	8.584	58.473	38.545	1.00 26.42	O
ATOM	2025	N	PHE	A	251	9.267	55.539	34.739	1.00 10.99	N
ATOM	2026	CA	PHE	A	251	9.939	55.730	33.457	1.00 10.73	C
ATOM	2027	C	PHE	A	251	8.889	56.060	32.372	1.00 11.00	C
ATOM	2028	O	PHE	A	251	9.074	57.076	31.639	1.00 11.60	O
ATOM	2029	CB	PHE	A	251	10.694	54.432	33.155	1.00 10.71	C
ATOM	2030	CG	PHE	A	251	11.544	54.433	31.882	1.00 11.29	C
ATOM	2031	CD1	PHE	A	251	12.829	54.963	31.890	1.00 11.44	C
ATOM	2032	CE1	PHE	A	251	13.685	54.893	30.746	1.00 10.81	C
ATOM	2033	CZ	PHE	A	251	13.245	54.234	29.630	1.00 12.41	C
ATOM	2034	CE2	PHE	A	251	11.949	53.671	29.601	1.00 13.51	C
ATOM	2035	CD2	PHE	A	251	11.108	53.752	30.772	1.00 13.44	C

FIGURE 4HH

ATOM	2036	N	LEU	A	252	7.841	55.248	32.255	1.00	9.80	N
ATOM	2037	CA	LEU	A	252	6.833	55.548	31.246	1.00	10.32	C
ATOM	2038	C	LEU	A	252	6.125	56.878	31.483	1.00	11.26	C
ATOM	2039	O	LEU	A	252	5.794	57.604	30.532	1.00	10.20	O
ATOM	2040	CB	LEU	A	252	5.785	54.407	31.248	1.00	12.14	C
ATOM	2041	CG	LEU	A	252	4.708	54.485	30.197	1.00	13.13	C
ATOM	2042	CD1	LEU	A	252	5.347	54.707	28.781	1.00	15.70	C
ATOM	2043	CD2	LEU	A	252	3.896	53.133	30.265	1.00	17.25	C
ATOM	2044	N	GLU	A	253	5.822	57.185	32.742	1.00	10.95	N
ATOM	2045	CA	GLU	A	253	5.103	58.425	33.061	1.00	12.42	C
ATOM	2046	C	GLU	A	253	5.942	59.671	32.803	1.00	12.33	C
ATOM	2047	O	GLU	A	253	5.362	60.772	32.693	1.00	16.37	O
ATOM	2048	CB	GLU	A	253	4.692	58.405	34.553	1.00	14.53	C
ATOM	2049	CG	GLU	A	253	3.477	57.515	34.759	1.00	19.54	C
ATOM	2050	CD	GLU	A	253	3.160	57.256	36.242	1.00	29.82	C
ATOM	2051	OE1	GLU	A	253	3.821	57.837	37.129	1.00	35.97	O
ATOM	2052	OE2	GLU	A	253	2.247	56.445	36.507	1.00	35.79	O
ATOM	2053	N	ARG	A	254	7.268	59.501	32.658	1.00	10.94	N
ATOM	2054	CA	ARG	A	254	8.090	60.616	32.211	1.00	9.95	C
ATOM	2055	C	ARG	A	254	8.027	60.827	30.685	1.00	10.51	O
ATOM	2056	O	ARG	A	254	8.375	61.885	30.209	1.00	11.14	O
ATOM	2057	CB	ARG	A	254	9.552	60.414	32.587	1.00	10.09	C
ATOM	2058	CG	ARG	A	254	9.801	60.451	34.150	1.00	11.47	C
ATOM	2059	CD	ARG	A	254	9.585	61.896	34.720	1.00	12.76	C
ATOM	2060	NE	ARG	A	254	10.392	62.945	34.055	1.00	12.48	N
ATOM	2061	CZ	ARG	A	254	9.880	64.010	33.407	1.00	9.08	C
ATOM	2062	NH1	ARG	A	254	10.713	64.865	32.868	1.00	11.66	N
ATOM	2063	NH2	ARG	A	254	8.550	64.208	33.253	1.00	13.63	N
ATOM	2064	N	MET	A	255	7.539	59.824	29.947	1.00	8.84	N
ATOM	2065	CA	MET	A	255	7.472	59.927	28.467	1.00	9.29	C
ATOM	2066	C	MET	A	255	6.090	60.424	28.029	1.00	8.46	C
ATOM	2067	O	MET	A	255	5.971	61.269	27.125	1.00	9.32	O
ATOM	2068	CB	BMET	A	255	7.752	58.542	27.828	0.35	8.95	C
ATOM	2069	CB	AMET	A	255	7.757	58.552	27.856	0.65	8.59	C
ATOM	2070	CG	BMET	A	255	9.033	57.829	28.294	0.35	11.26	C
ATOM	2071	CG	AMET	A	255	9.150	58.127	28.125	0.65	11.34	C
ATOM	2072	SD	BMET	A	255	9.118	56.082	27.725	0.35	13.20	S
ATOM	2073	SD	AMET	A	255	9.526	56.749	27.065	0.65	13.97	S
ATOM	2074	CE	BMET	A	255	10.893	55.888	27.580	0.35	16.06	C
ATOM	2075	CE	AMET	A	255	10.390	55.756	28.119	0.65	18.05	C
ATOM	2076	N	LEU	A	256	5.034	59.862	28.628	1.00	10.19	N
ATOM	2077	CA	LEU	A	256	3.666	60.149	28.232	1.00	9.88	C
ATOM	2078	C	LEU	A	256	3.121	61.321	29.051	1.00	10.86	C
ATOM	2079	O	LEU	A	256	2.355	61.175	30.010	1.00	12.08	O
ATOM	2080	CB	LEU	A	256	2.758	58.918	28.325	1.00	10.28	C
ATOM	2081	CG	LEU	A	256	3.237	57.810	27.377	1.00	10.63	C
ATOM	2082	CD1	LEU	A	256	2.377	56.581	27.568	1.00	13.07	C
ATOM	2083	CD2	LEU	A	256	3.116	58.340	25.984	1.00	10.61	C
ATOM	2084	N	VAL	A	257	3.640	62.466	28.706	1.00	8.53	N
ATOM	2085	CA	VAL	A	257	3.300	63.746	29.395	1.00	9.01	C
ATOM	2086	C	VAL	A	257	2.833	64.692	28.296	1.00	9.52	C
ATOM	2087	O	VAL	A	257	3.571	64.833	27.280	1.00	9.82	O
ATOM	2088	CB	VAL	A	257	4.611	64.285	29.994	1.00	12.13	C
ATOM	2089	CG1	VAL	A	257	4.413	65.721	30.554	1.00	12.60	C
ATOM	2090	CG2	VAL	A	257	5.102	63.361	31.078	1.00	12.28	C
ATOM	2091	N	ARG	A	258	1.646	65.310	28.409	1.00	8.71	N
ATOM	2092	CA	ARG	A	258	1.168	66.205	27.365	1.00	8.96	C
ATOM	2093	C	ARG	A	258	2.057	67.397	27.157	1.00	11.25	C
ATOM	2094	O	ARG	A	258	2.288	67.770	25.973	1.00	12.22	O
ATOM	2095	CB	ARG	A	258	-0.290	66.685	27.603	1.00	9.62	C

FIGURE 4II

ATOM	2096	CG	ARG	A	258	-1.362	65.599	27.476	1.00	12.12	C
ATOM	2097	CD	ARG	A	258	-2.794	66.123	27.569	1.00	12.75	C
ATOM	2098	NE	ARG	A	258	-2.981	67.106	26.533	1.00	11.22	N
ATOM	2099	CZ	ARG	A	258	-3.287	66.808	25.262	1.00	9.89	C
ATOM	2100	NH1	ARG	A	258	-3.572	65.537	24.905	1.00	9.72	N
ATOM	2101	NH2	ARG	A	258	-3.353	67.801	24.365	1.00	11.46	N
ATOM	2102	N	ASP	A	259	2.481	68.043	28.259	1.00	10.31	N
ATOM	2103	CA	ASP	A	259	3.277	69.275	28.096	1.00	13.08	C
ATOM	2104	C	ASP	A	259	4.669	68.911	27.622	1.00	11.76	C
ATOM	2105	O	ASP	A	259	5.389	68.196	28.324	1.00	11.51	O
ATOM	2106	CB	ASP	A	259	3.367	70.018	29.459	1.00	13.39	C
ATOM	2107	CG	ASP	A	259	4.096	71.349	29.380	1.00	23.83	C
ATOM	2108	OD1	ASP	A	259	4.843	71.624	28.427	1.00	27.23	O
ATOM	2109	OD2	ASP	A	259	3.974	72.190	30.300	1.00	28.54	O
ATOM	2110	N	PRO	A	260	5.055	69.328	26.428	1.00	12.33	N
ATOM	2111	CA	PRO	A	260	6.360	68.882	25.908	1.00	13.56	C
ATOM	2112	C	PRO	A	260	7.544	69.396	26.697	1.00	16.64	C
ATOM	2113	O	PRO	A	260	8.579	68.730	26.620	1.00	17.54	O
ATOM	2114	CB	PRO	A	260	6.421	69.440	24.460	1.00	14.17	C
ATOM	2115	CG	PRO	A	260	5.067	70.008	24.211	1.00	18.15	C
ATOM	2116	CD	PRO	A	260	4.284	70.159	25.491	1.00	13.55	C
ATOM	2117	N	GLN	A	261	7.421	70.543	27.408	1.00	16.15	N
ATOM	2118	CA	GLN	A	261	8.545	71.085	28.213	1.00	18.11	C
ATOM	2119	C	GLN	A	261	8.695	70.252	29.500	1.00	17.29	C
ATOM	2120	O	GLN	A	261	9.810	70.189	30.053	1.00	20.10	O
ATOM	2121	CB	GLN	A	261	8.319	72.578	28.568	1.00	19.35	C
ATOM	2122	CG	GLN	A	261	8.482	73.464	27.326	1.00	26.81	C
ATOM	2123	CD	GLN	A	261	7.829	74.848	27.425	1.00	36.36	C
ATOM	2124	OE1	GLN	A	261	7.680	75.425	28.518	1.00	42.01	O
ATOM	2125	NE2	GLN	A	261	7.439	75.385	26.268	1.00	39.98	N
ATOM	2126	N	GLU	A	262	7.614	69.610	29.951	1.00	13.53	N
ATOM	2127	CA	GLU	A	262	7.673	68.770	31.175	1.00	12.61	C
ATOM	2128	C	GLU	A	262	8.098	67.311	30.859	1.00	12.36	C
ATOM	2129	O	GLU	A	262	8.604	66.568	31.693	1.00	12.06	O
ATOM	2130	CB	BGLU	A	262	6.378	68.867	31.979	0.25	13.67	C
ATOM	2131	CB	AGLU	A	262	6.252	68.712	31.755	0.75	13.17	C
ATOM	2132	CG	BGLU	A	262	6.058	70.315	32.350	0.25	16.05	C
ATOM	2133	CG	AGLU	A	262	5.999	67.839	33.001	0.75	20.15	C
ATOM	2134	CD	BGLU	A	262	5.380	70.491	33.692	0.25	20.99	C
ATOM	2135	CD	AGLU	A	262	4.499	67.713	33.426	0.75	23.66	C
ATOM	2136	OE1	BGLU	A	262	4.275	69.946	33.881	0.25	22.46	O
ATOM	2137	OE1	AGLU	A	262	3.605	68.438	32.919	0.75	23.00	O
ATOM	2138	OE2	BGLU	A	262	5.950	71.192	34.569	0.25	22.29	O
ATOM	2139	OE2	AGLU	A	262	4.185	66.828	34.253	0.75	26.78	O
ATOM	2140	N	ARG	A	263	7.836	66.916	29.632	1.00	11.27	N
ATOM	2141	CA	ARG	A	263	8.249	65.608	29.151	1.00	10.67	C
ATOM	2142	C	ARG	A	263	9.746	65.363	29.276	1.00	9.00	C
ATOM	2143	O	ARG	A	263	10.577	66.241	29.034	1.00	11.31	O
ATOM	2144	CB	ARG	A	263	7.799	65.513	27.666	1.00	10.63	C
ATOM	2145	CG	ARG	A	263	7.801	64.050	27.142	1.00	9.46	C
ATOM	2146	CD	ARG	A	263	7.252	63.895	25.701	1.00	8.86	C
ATOM	2147	NE	ARG	A	263	5.920	64.511	25.624	1.00	8.65	N
ATOM	2148	CZ	ARG	A	263	5.430	65.131	24.541	1.00	7.25	C
ATOM	2149	NH1	ARG	A	263	4.223	65.712	24.568	1.00	7.82	N
ATOM	2150	NH2	ARG	A	263	6.197	65.162	23.396	1.00	7.55	N
ATOM	2151	N	ALA	A	264	10.141	64.130	29.617	1.00	9.24	N
ATOM	2152	CA	ALA	A	264	11.569	63.790	29.689	1.00	8.75	C
ATOM	2153	C	ALA	A	264	12.282	63.886	28.329	1.00	10.29	C
ATOM	2154	O	ALA	A	264	11.652	63.654	27.278	1.00	12.39	O
ATOM	2155	CB	ALA	A	264	11.769	62.358	30.245	1.00	10.59	C

FIGURE 4JJ

ATOM	2156	N	THR A 265	13.555	64.303	28.364	1.00	12.07	N
ATOM	2157	CA	THR A 265	14.397	64.195	27.178	1.00	11.22	C
ATOM	2158	C	THR A 265	15.015	62.814	27.145	1.00	9.84	C
ATOM	2159	O	THR A 265	15.014	62.018	28.127	1.00	10.00	O
ATOM	2160	CB	THR A 265	15.537	65.184	27.215	1.00	11.32	C
ATOM	2161	OG1	THR A 265	16.342	64.868	28.387	1.00	14.65	O
ATOM	2162	CG2	THR A 265	15.021	66.639	27.343	1.00	12.42	C
ATOM	2163	N	ALA A 266	15.579	62.451	25.973	1.00	9.51	N
ATOM	2164	CA	ALA A 266	16.215	61.130	25.850	1.00	9.32	C
ATOM	2165	C	ALA A 266	17.363	60.981	26.851	1.00	9.81	C
ATOM	2166	O	ALA A 266	17.492	59.932	27.449	1.00	12.03	O
ATOM	2167	CB	ALA A 266	16.742	60.880	24.384	1.00	8.46	C
ATOM	2168	N	GLN A 267	18.132	62.052	27.079	1.00	11.17	N
ATOM	2169	CA	GLN A 267	19.220	61.971	28.012	1.00	11.55	C
ATOM	2170	C	GLN A 267	18.700	61.745	29.444	1.00	12.69	C
ATOM	2171	O	GLN A 267	19.280	60.937	30.197	1.00	13.32	O
ATOM	2172	CB	GLN A 267	20.064	63.257	27.967	1.00	14.77	C
ATOM	2173	CG	GLN A 267	21.347	63.092	28.828	1.00	17.49	C
ATOM	2174	CD	GLN A 267	22.231	61.940	28.381	1.00	18.90	C
ATOM	2175	OE1	GLN A 267	22.614	61.897	27.218	1.00	18.69	O
ATOM	2176	NE2	GLN A 267	22.513	60.975	29.283	1.00	18.42	N
ATOM	2177	N	GLU A 268	17.615	62.418	29.820	1.00	11.27	N
ATOM	2178	CA	GLU A 268	17.057	62.158	31.178	1.00	12.74	C
ATOM	2179	C	GLU A 268	16.644	60.672	31.358	1.00	11.29	C
ATOM	2180	O	GLU A 268	16.904	60.027	32.396	1.00	13.40	O
ATOM	2181	CB	GLU A 268	15.842	63.090	31.443	1.00	11.01	C
ATOM	2182	CG	GLU A 268	15.255	62.851	32.880	1.00	14.18	C
ATOM	2183	CD	GLU A 268	13.938	63.542	33.201	1.00	18.01	C
ATOM	2184	OE1	GLU A 268	13.241	63.063	34.149	1.00	17.51	O
ATOM	2185	OE2	GLU A 268	13.572	64.501	32.526	1.00	18.85	O
ATOM	2186	N	LEU A 269	16.054	60.103	30.306	1.00	10.15	N
ATOM	2187	CA	LEU A 269	15.645	58.723	30.362	1.00	9.80	C
ATOM	2188	C	LEU A 269	16.850	57.766	30.401	1.00	10.14	C
ATOM	2189	O	LEU A 269	16.814	56.743	31.090	1.00	11.10	O
ATOM	2190	CB	LEU A 269	14.716	58.393	29.167	1.00	9.81	C
ATOM	2191	CG	LEU A 269	13.407	59.175	29.265	1.00	10.43	C
ATOM	2192	CD1	LEU A 269	12.754	59.204	27.883	1.00	11.29	C
ATOM	2193	CD2	LEU A 269	12.411	58.599	30.348	1.00	12.24	C
ATOM	2194	N	LEU A 270	17.920	58.083	29.681	1.00	11.42	N
ATOM	2195	CA	LEU A 270	19.140	57.290	29.768	1.00	11.94	C
ATOM	2196	C	LEU A 270	19.687	57.253	31.204	1.00	13.97	C
ATOM	2197	O	LEU A 270	20.327	56.258	31.621	1.00	14.83	O
ATOM	2198	CB	LEU A 270	20.213	57.866	28.835	1.00	13.11	C
ATOM	2199	CG	LEU A 270	20.063	57.427	27.368	1.00	12.33	C
ATOM	2200	CD1	LEU A 270	21.227	58.082	26.641	1.00	12.47	C
ATOM	2201	CD2	LEU A 270	20.149	55.866	27.222	1.00	12.27	C
ATOM	2202	N	ASP A 271	19.422	58.327	31.945	1.00	11.74	N
ATOM	2203	CA	ASP A 271	19.906	58.455	33.300	1.00	14.17	C
ATOM	2204	C	ASP A 271	18.970	57.850	34.345	1.00	14.46	C
ATOM	2205	O	ASP A 271	19.232	57.956	35.560	1.00	15.38	O
ATOM	2206	CB	ASP A 271	20.095	59.949	33.608	1.00	14.67	C
ATOM	2207	CG	ASP A 271	21.229	60.589	32.795	1.00	18.70	C
ATOM	2208	OD1	ASP A 271	22.119	59.824	32.328	1.00	21.12	O
ATOM	2209	OD2	ASP A 271	21.299	61.831	32.586	1.00	21.41	O
ATOM	2210	N	HIS A 272	17.863	57.263	33.895	1.00	12.27	N
ATOM	2211	CA	HIS A 272	16.794	56.833	34.812	1.00	12.23	C
ATOM	2212	C	HIS A 272	17.131	55.483	35.410	1.00	12.60	C
ATOM	2213	O	HIS A 272	17.663	54.598	34.699	1.00	13.50	O
ATOM	2214	CB	HIS A 272	15.508	56.658	34.012	1.00	12.53	C
ATOM	2215	CG	HIS A 272	14.277	56.535	34.846	1.00	12.61	C

FIGURE 4KK

ATOM	2216	ND1	HIS	A	272	13.874	55.337	35.396	1.00	10.96	N
ATOM	2217	CE1	HIS	A	272	12.725	55.521	36.031	1.00	10.40	C
ATOM	2218	NE2	HIS	A	272	12.404	56.810	35.965	1.00	11.35	N
ATOM	2219	CD2	HIS	A	272	13.348	57.462	35.211	1.00	11.85	C
ATOM	2220	N	PRO	A	273	16.784	55.235	36.675	1.00	13.62	N
ATOM	2221	CA	PRO	A	273	17.104	53.947	37.300	1.00	14.95	C
ATOM	2222	C	PRO	A	273	16.476	52.713	36.645	1.00	12.35	C
ATOM	2223	O	PRO	A	273	17.017	51.628	36.825	1.00	14.80	O
ATOM	2224	CB	PRO	A	273	16.608	54.102	38.752	1.00	16.16	C
ATOM	2225	CG	PRO	A	273	16.095	55.471	38.910	1.00	19.63	C
ATOM	2226	CD	PRO	A	273	16.166	56.217	37.604	1.00	15.13	C
ATOM	2227	N	PHE	A	274	15.432	52.854	35.821	1.00	11.42	N
ATOM	2228	CA	PHE	A	274	14.877	51.667	35.176	1.00	12.37	C
ATOM	2229	C	PHE	A	274	15.995	51.014	34.323	1.00	11.96	C
ATOM	2230	O	PHE	A	274	16.050	49.765	34.208	1.00	14.11	O
ATOM	2231	CB	PHE	A	274	13.670	52.047	34.269	1.00	12.80	C
ATOM	2232	CG	PHE	A	274	13.199	50.896	33.425	1.00	10.87	C
ATOM	2233	CD1	PHE	A	274	12.766	49.719	34.015	1.00	13.43	C
ATOM	2234	CE1	PHE	A	274	12.321	48.643	33.226	1.00	15.05	C
ATOM	2235	CZ	PHE	A	274	12.331	48.723	31.854	1.00	13.17	C
ATOM	2236	CE2	PHE	A	274	12.761	49.862	31.235	1.00	12.76	C
ATOM	2237	CD2	PHE	A	274	13.184	50.990	32.026	1.00	12.05	C
ATOM	2238	N	LEU	A	275	16.819	51.836	33.675	1.00	13.51	N
ATOM	2239	CA	LEU	A	275	17.850	51.318	32.797	1.00	16.21	C
ATOM	2240	C	LEU	A	275	19.018	50.613	33.506	1.00	18.22	C
ATOM	2241	O	LEU	A	275	19.859	50.023	32.852	1.00	19.03	O
ATOM	2242	CB	LEU	A	275	18.305	52.335	31.758	1.00	15.72	C
ATOM	2243	CG	LEU	A	275	17.136	52.823	30.875	1.00	16.68	C
ATOM	2244	CD1	LEU	A	275	17.697	53.751	29.816	1.00	16.32	C
ATOM	2245	CD2	LEU	A	275	16.396	51.667	30.195	1.00	15.77	C
ATOM	2246	N	LEU	A	276	19.008	50.599	34.851	1.00	19.65	N
ATOM	2247	CA	LEU	A	276	19.892	49.652	35.576	1.00	21.14	C
ATOM	2248	C	LEU	A	276	19.523	48.202	35.304	1.00	20.14	C
ATOM	2249	O	LEU	A	276	20.318	47.290	35.571	1.00	21.20	O
ATOM	2250	CB	LEU	A	276	19.830	49.899	37.085	1.00	20.89	C
ATOM	2251	CG	LEU	A	276	20.178	51.328	37.553	1.00	24.72	C
ATOM	2252	CD1	LEU	A	276	19.809	51.445	39.036	1.00	27.85	C
ATOM	2253	CD2	LEU	A	276	21.636	51.683	37.306	1.00	27.39	C
ATOM	2254	N	GLN	A	277	18.310	47.961	34.802	1.00	18.01	N
ATOM	2255	CA	GLN	A	277	17.825	46.626	34.468	1.00	19.00	C
ATOM	2256	C	GLN	A	277	18.214	46.131	33.074	1.00	19.15	C
ATOM	2257	O	GLN	A	277	17.840	45.013	32.705	1.00	18.88	O
ATOM	2258	CB	GLN	A	277	16.292	46.543	34.633	1.00	19.70	C
ATOM	2259	CG	GLN	A	277	15.883	46.521	36.112	1.00	22.51	C
ATOM	2260	CD	GLN	A	277	14.415	46.848	36.339	1.00	24.20	C
ATOM	2261	OE1	GLN	A	277	14.078	47.918	36.866	1.00	26.83	O
ATOM	2262	NE2	GLN	A	277	13.535	45.924	35.952	1.00	28.13	N
ATOM	2263	N	THR	A	278	18.987	46.926	32.331	1.00	17.92	N
ATOM	2264	CA	THR	A	278	19.324	46.608	30.905	1.00	21.03	C
ATOM	2265	C	THR	A	278	20.091	45.284	30.863	1.00	22.47	C
ATOM	2266	O	THR	A	278	20.978	45.061	31.704	1.00	24.27	O
ATOM	2267	CB	THR	A	278	20.169	47.742	30.294	1.00	20.39	C
ATOM	2268	OG1	THR	A	278	19.426	48.972	30.304	1.00	23.31	O
ATOM	2269	CG2	THR	A	278	20.419	47.550	28.813	1.00	23.41	C
ATOM	2270	N	GLY	A	279	19.736	44.380	29.952	1.00	23.07	N
ATOM	2271	CA	GLY	A	279	20.435	43.089	29.864	1.00	25.39	C
ATOM	2272	C	GLY	A	279	21.391	43.132	28.691	1.00	26.73	C
ATOM	2273	O	GLY	A	279	21.547	44.179	28.045	1.00	27.80	O
ATOM	2274	N	LEU	A	280	22.015	42.005	28.400	1.00	29.48	N
ATOM	2275	CA	LEU	A	280	22.946	41.920	27.268	1.00	30.73	C

FIGURE 4LL

ATOM	2276	C	LEU	A	280	22.130	41.621	26.034	1.00	30.92	C
ATOM	2277	O	LEU	A	280	21.051	41.067	26.157	1.00	30.61	O
ATOM	2278	CB	LEU	A	280	23.924	40.779	27.495	1.00	31.98	C
ATOM	2279	CG	LEU	A	280	24.759	40.843	28.764	1.00	33.36	C
ATOM	2280	CD1	LEU	A	280	25.426	39.482	29.016	1.00	39.58	C
ATOM	2281	CD2	LEU	A	280	25.784	41.945	28.642	1.00	36.61	C
ATOM	2282	N	PRO	A	281	22.629	41.991	24.851	1.00	33.08	N
ATOM	2283	CA	PRO	A	281	21.961	41.634	23.583	1.00	33.40	C
ATOM	2284	C	PRO	A	281	21.477	40.190	23.544	1.00	33.26	C
ATOM	2285	O	PRO	A	281	20.406	39.902	22.974	1.00	31.95	O
ATOM	2286	CB	PRO	A	281	23.074	41.836	22.544	1.00	34.90	C
ATOM	2287	CG	PRO	A	281	23.899	42.993	23.120	1.00	33.86	C
ATOM	2288	CD	PRO	A	281	23.826	42.835	24.624	1.00	33.62	C
ATOM	2289	N	GLU	A	282	22.240	39.289	24.163	1.00	32.07	N
ATOM	2290	CA	GLU	A	282	21.864	37.893	24.200	1.00	31.48	C
ATOM	2291	C	GLU	A	282	20.517	37.618	24.865	1.00	29.03	C
ATOM	2292	O	GLU	A	282	19.957	36.575	24.594	1.00	30.91	O
ATOM	2293	CB	GLU	A	282	22.945	37.028	24.854	1.00	34.18	C
ATOM	2294	CG	GLU	A	282	24.324	37.165	24.217	1.00	39.89	C
ATOM	2295	CD	GLU	A	282	25.183	38.200	24.943	1.00	44.46	C
ATOM	2296	OE1	GLU	A	282	25.705	37.875	26.044	1.00	47.77	O
ATOM	2297	OE2	GLU	A	282	25.322	39.337	24.418	1.00	44.88	O
ATOM	2298	N	CYS	A	283	19.975	38.526	25.700	1.00	26.92	N
ATOM	2299	CA	CYS	A	283	18.639	38.290	26.281	1.00	26.38	C
ATOM	2300	C	CYS	A	283	17.524	38.297	25.240	1.00	24.27	C
ATOM	2301	O	CYS	A	283	16.415	37.821	25.516	1.00	25.85	O
ATOM	2302	CB	CYS	A	283	18.279	39.240	27.453	1.00	26.62	C
ATOM	2303	SG	CYS	A	283	17.905	41.001	27.096	1.00	29.93	S
ATOM	2304	N	LEU	A	284	17.806	38.854	24.056	1.00	20.18	N
ATOM	2305	CA	LEU	A	284	16.806	38.882	22.984	1.00	18.11	C
ATOM	2306	C	LEU	A	284	16.984	37.754	21.954	1.00	16.18	C
ATOM	2307	O	LEU	A	284	16.094	37.498	21.159	1.00	17.35	O
ATOM	2308	CB	LEU	A	284	16.833	40.239	22.252	1.00	18.37	C
ATOM	2309	CG	LEU	A	284	16.534	41.433	23.168	1.00	19.77	C
ATOM	2310	CD1	LEU	A	284	16.680	42.728	22.354	1.00	23.74	C
ATOM	2311	CD2	LEU	A	284	15.121	41.313	23.726	1.00	20.69	C
ATOM	2312	N	VAL	A	285	18.127	37.086	21.953	1.00	15.08	N
ATOM	2313	CA	VAL	A	285	18.468	36.247	20.833	1.00	15.31	C
ATOM	2314	C	VAL	A	285	17.519	35.038	20.690	1.00	15.94	C
ATOM	2315	O	VAL	A	285	17.107	34.683	19.589	1.00	17.34	O
ATOM	2316	CB	VAL	A	285	19.973	35.825	20.905	1.00	16.94	C
ATOM	2317	CG1	VAL	A	285	20.270	34.706	19.900	1.00	16.98	C
ATOM	2318	CG2	VAL	A	285	20.854	37.019	20.602	1.00	18.86	C
ATOM	2319	N	PRO	A	286	17.176	34.351	21.762	1.00	18.00	N
ATOM	2320	CA	PRO	A	286	16.255	33.206	21.583	1.00	19.06	C
ATOM	2321	C	PRO	A	286	14.907	33.608	20.978	1.00	17.63	C
ATOM	2322	O	PRO	A	286	14.346	32.870	20.174	1.00	18.09	O
ATOM	2323	CB	PRO	A	286	16.073	32.652	22.991	1.00	20.10	C
ATOM	2324	CG	PRO	A	286	17.314	33.136	23.719	1.00	21.99	C
ATOM	2325	CD	PRO	A	286	17.682	34.479	23.137	1.00	20.86	C
ATOM	2326	N	LEU	A	287	14.389	34.773	21.373	1.00	15.33	N
ATOM	2327	CA	LEU	A	287	13.149	35.217	20.756	1.00	15.70	C
ATOM	2328	C	LEU	A	287	13.270	35.574	19.285	1.00	14.54	C
ATOM	2329	O	LEU	A	287	12.375	35.288	18.484	1.00	16.05	O
ATOM	2330	CB	LEU	A	287	12.562	36.392	21.550	1.00	14.49	C
ATOM	2331	CG	LEU	A	287	12.067	36.039	22.972	1.00	17.22	C
ATOM	2332	CD1	LEU	A	287	11.677	37.326	23.670	1.00	17.60	C
ATOM	2333	CD2	LEU	A	287	10.902	35.071	22.931	1.00	18.92	C
ATOM	2334	N	ILE	A	288	14.386	36.211	18.943	1.00	13.83	N
ATOM	2335	CA	ILE	A	288	14.626	36.573	17.566	1.00	16.13	C

FIGURE 4MM

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ATOM    2336  C    ILE  A  288    14.615  35.278  16.745  1.00  16.83        C
ATOM    2337  O    ILE  A  288    13.996  35.238  15.695  1.00  18.71        O
ATOM    2338  CB   ILE  A  288    15.959  37.356  17.463  1.00  14.80        C
ATOM    2339  CG1  ILE  A  288    15.758  38.765  18.063  1.00  15.30        C
ATOM    2340  CD1  ILE  A  288    17.100  39.467  18.324  1.00  15.82        C
ATOM    2341  CG2  ILE  A  288    16.405  37.438  15.992  1.00  18.31        C
ATOM    2342  N    GLN  A  289    15.263  34.231  17.252  1.00  18.22        N
ATOM    2343  CA   GLN  A  289    15.311  32.953  16.534  1.00  21.15        C
ATOM    2344  C    GLN  A  289    13.922  32.317  16.398  1.00  23.19        C
ATOM    2345  O    GLN  A  289    13.591  31.793  15.341  1.00  25.06        O
ATOM    2346  CB   GLN  A  289    16.339  32.008  17.165  1.00  24.24        C
ATOM    2347  CG   GLN  A  289    17.761  32.543  17.075  1.00  29.01        C
ATOM    2348  CD   GLN  A  289    18.830  31.706  17.798  1.00  37.48        C
ATOM    2349  OE1  GLN  A  289    18.536  30.948  18.737  1.00  39.07        O
ATOM    2350  NE2  GLN  A  289    20.090  31.872  17.370  1.00  37.51        N
ATOM    2351  N    LEU  A  290    13.073  32.426  17.425  1.00  21.62        N
ATOM    2352  CA   LEU  A  290    11.710  31.851  17.323  1.00  22.73        C
ATOM    2353  C    LEU  A  290    10.745  32.583  16.397  1.00  23.02        C
ATOM    2354  O    LEU  A  290     9.826  31.970  15.843  1.00  24.60        O
ATOM    2355  CB   LEU  A  290    11.117  31.720  18.726  1.00  22.22        C
ATOM    2356  CG   LEU  A  290    11.829  30.696  19.606  1.00  25.78        C
ATOM    2357  CD1  LEU  A  290    11.312  30.809  21.029  1.00  25.45        C
ATOM    2358  CD2  LEU  A  290    11.590  29.257  18.993  1.00  29.01        C
ATOM    2359  N    TYR  A  291    10.932  33.885  16.233  1.00  20.52        N
ATOM    2360  CA   TYR  A  291     9.953  34.729  15.550  1.00  20.95        C
ATOM    2361  C    TYR  A  291    10.362  35.555  14.303  1.00  25.40        C
ATOM    2362  O    TYR  A  291     9.479  36.057  13.635  1.00  27.58        O
ATOM    2363  CB   TYR  A  291     9.326  35.709  16.548  1.00  17.96        C
ATOM    2364  CG   TYR  A  291     8.504  35.040  17.616  1.00  12.71        C
ATOM    2365  CD1  TYR  A  291     9.009  34.877  18.896  1.00  11.98        C
ATOM    2366  CE1  TYR  A  291     8.225  34.231  19.885  1.00  12.13        C
ATOM    2367  CZ   TYR  A  291     6.957  33.787  19.540  1.00  11.48        C
ATOM    2368  OH   TYR  A  291     6.155  33.157  20.474  1.00  13.73        O
ATOM    2369  CE2  TYR  A  291     6.433  33.938  18.276  1.00  14.58        C
ATOM    2370  CD2  TYR  A  291     7.211  34.574  17.317  1.00  17.15        C
ATOM    2371  N    ARG  A  292    11.644  35.824  14.051  1.00  31.50        N
ATOM    2372  CA   ARG  A  292    11.994  36.769  12.931  1.00  36.97        C
ATOM    2373  C    ARG  A  292    11.375  36.347  11.582  1.00  39.86        C
ATOM    2374  O    ARG  A  292    10.925  37.195  10.795  1.00  43.25        O
ATOM    2375  CB   ARG  A  292    13.515  36.954  12.783  1.00  37.31        C
ATOM    2376  CG   ARG  A  292    14.222  35.745  12.154  1.00  38.16        C
ATOM    2377  CD   ARG  A  292    15.723  35.726  12.304  1.00  41.67        C
ATOM    2378  NE   ARG  A  292    16.266  34.515  11.674  1.00  43.48        N
ATOM    2379  CZ   ARG  A  292    16.717  34.461  10.419  1.00  44.76        C
ATOM    2380  NH1  ARG  A  292    17.173  33.320   9.938  1.00  45.90        N
ATOM    2381  NH2  ARG  A  292    16.724  35.545   9.643  1.00  43.30        N
ATOM    2382  N    LYS  A  293    11.425  35.040  11.329  1.00  42.64        N
ATOM    2383  CA   LYS  A  293    10.654  34.344  10.322  1.00  45.60        C
ATOM    2384  C    LYS  A  293    10.390  32.998  10.996  1.00  47.37        C
ATOM    2385  O    LYS  A  293    10.933  32.729  12.081  1.00  47.49        O
ATOM    2386  CB   LYS  A  293    11.435  34.165   9.003  1.00  46.86        C
TER     2387       LYS  A  293
ATOM    2388  N    GLY  W    1     1.793  46.757  18.751  1.00  17.14        N
ATOM    2389  CA   GLY  W    1     1.528  46.556  17.315  1.00  25.77        C
ATOM    2390  C    GLY  W    1     0.951  45.176  17.042  1.00  29.23        C
ATOM    2391  O    GLY  W    1     0.843  44.363  17.993  1.00  28.85        O
ATOM    2392  OXT  GLY  W    1     0.621  44.889  15.838  1.00  32.49        O
HETATM  2393  O    HOH  W    2    22.188  40.692  11.498  1.00  11.89        O
HETATM  2394  O    HOH  W    3    15.794  64.253  23.801  1.00   9.88        O
HETATM  2395  O    HOH  W    4     8.355  59.596  16.556  1.00  10.82        O
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FIGURE 4NN

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HETATM 2396  O    HOH W   5      0.251  58.665  20.369  1.00 10.14          O
HETATM 2397  O    HOH W   6     -3.377  61.809  24.836  1.00 13.83          O
HETATM 2398  O    HOH W   7      5.153  62.069  17.436  1.00 12.04          O
HETATM 2399  O    HOH W   8     10.941  58.764  10.011  1.00 13.04          O
HETATM 2400  O    HOH W   9     12.472  67.030   6.773  1.00 14.71          O
HETATM 2401  O    HOH W  10     20.528  64.429  23.559  1.00 14.36          O
HETATM 2402  O    HOH W  11     24.360  54.889  11.681  1.00 11.45          O
HETATM 2403  O    HOH W  12     10.807  76.885  12.998  1.00 18.42          O
HETATM 2404  O    HOH W  13     11.294  63.640   5.849  1.00 13.10          O
HETATM 2405  O    HOH W  14     13.839  66.279  23.729  1.00 15.51          O
HETATM 2406  O    HOH W  15     18.311  64.329  25.078  1.00 13.78          O
HETATM 2407  O    HOH W  16      0.285  65.141  30.954  1.00 12.28          O
HETATM 2408  O    HOH W  17     27.953  46.434 -10.447  1.00 13.76          O
HETATM 2409  O    HOH W  18     11.595  65.584  25.348  1.00 16.11          O
HETATM 2410  O    HOH W  19     17.388  65.851 -14.665  1.00 20.06          O
HETATM 2411  O    HOH W  20      6.621  42.678  24.591  1.00 15.50          O
HETATM 2412  O    HOH W  21      1.428  67.642  30.959  1.00 14.12          O
HETATM 2413  O    HOH W  22     16.273  60.020  35.189  1.00 17.00          O
HETATM 2414  O    HOH W  23      4.051  58.864  14.885  1.00 15.77          O
HETATM 2415  O    HOH W  24      3.980  43.082  23.753  1.00 19.15          O
HETATM 2416  O    HOH W  25     -2.293  55.387  20.951  1.00 19.34          O
HETATM 2417  O    HOH W  26     24.905  51.099  12.739  1.00 15.53          O
HETATM 2418  O    HOH W  27      5.194  61.579  14.666  1.00 19.85          O
HETATM 2419  O    HOH W  28     26.688  39.918  -9.461  1.00 18.05          O
HETATM 2420  O    HOH W  29     -4.828  59.634  25.600  1.00 17.12          O
HETATM 2421  O    HOH W  30      4.555  36.259  26.473  1.00 19.73          O
HETATM 2422  O    HOH W  31      2.529  32.398  17.591  1.00 17.16          O
HETATM 2423  O    HOH W  32     25.196  59.428  -8.087  1.00 17.22          O
HETATM 2424  O    HOH W  33     10.259  69.530 -15.733  1.00 18.49          O
HETATM 2425  O    HOH W  34     -5.495  49.278  22.481  1.00 18.77          O
HETATM 2426  O    HOH W  35     13.200  41.116  34.035  1.00 21.08          O
HETATM 2427  O    HOH W  36      7.124  69.221  21.128  1.00 19.75          O
HETATM 2428  O    HOH W  37     11.096  67.877  26.979  1.00 16.47          O
HETATM 2429  O    HOH W  38     20.313  54.738  33.912  1.00 17.96          O
HETATM 2430  O    HOH W  39      5.292  71.689  21.059  1.00 18.19          O
HETATM 2431  O    HOH W  40      5.131  56.479  14.657  1.00 17.35          O
HETATM 2432  O    HOH W  41      5.592  37.239  14.695  1.00 21.14          O
HETATM 2433  O    HOH W  42     -2.646  49.180  25.180  1.00 19.53          O
HETATM 2434  O    HOH W  43     18.978  37.507  -7.833  1.00 21.82          O
HETATM 2435  O    HOH W  44      6.177  62.808  34.479  1.00 19.85          O
HETATM 2436  O    HOH W  45     26.614  58.473   7.610  1.00 18.33          O
HETATM 2437  O    HOH W  46     13.874  61.347  36.062  1.00 23.02          O
HETATM 2438  O    HOH W  47      1.568  68.792   7.479  1.00 23.92          O
HETATM 2439  O    HOH W  48     25.877  45.862   6.070  1.00 20.75          O
HETATM 2440  O    HOH W  49     15.640  54.659   6.838  1.00 23.63          O
HETATM 2441  O    HOH W  50     20.971  56.183   8.467  1.00 18.33          O
HETATM 2442  O    HOH W  51     29.403  39.540  -9.354  1.00 20.57          O
HETATM 2443  O    HOH W  52      9.752  67.579   5.855  1.00 22.81          O
HETATM 2444  O    HOH W  53      5.675  43.021  28.715  1.00 19.15          O
HETATM 2445  O    HOH W  54     11.552  60.299  37.214  1.00 22.94          O
HETATM 2446  O    HOH W  55      8.846  64.765   6.410  1.00 23.10          O
HETATM 2447  O    HOH W  56     10.737  61.436 -10.110  1.00 20.69          O
HETATM 2448  O    HOH W  57     20.710  47.717  24.838  1.00 23.85          O
HETATM 2449  O    HOH W  58      6.577  57.159   1.317  1.00 22.88         .O
HETATM 2450  O    HOH W  59      8.863  57.900  -0.207  1.00 22.83          O
HETATM 2451  O    HOH W  60     -7.001  51.952  24.530  1.00 26.02          O
HETATM 2452  O    HOH W  61     15.181  30.222  20.408  1.00 26.01          O
HETATM 2453  O    HOH W  62      9.734  67.562 -17.572  1.00 23.70          O
HETATM 2454  O    HOH W  63      7.452  72.773   9.664  1.00 25.11          O
HETATM 2455  O    HOH W  64     29.691  52.090  -2.811  1.00 29.20          O
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FIGURE 4OO

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HETATM 2456  O    HOH W  65    23.214  56.664   9.869  1.00  25.15         O
HETATM 2457  O    HOH W  66     9.978  41.338  34.428  1.00  23.35         O
HETATM 2458  O    HOH W  67    17.960  53.770   8.850  1.00  20.10         O
HETATM 2459  O    HOH W  68    27.843  54.821  18.015  1.00  25.79         O
HETATM 2460  O    HOH W  69     0.997  71.427   9.731  1.00  23.46         O
HETATM 2461  O    HOH W  70    25.317  37.682  -8.783  1.00  28.36         O
HETATM 2462  O    HOH W  71    13.075  58.354   2.682  1.00  20.02         O
HETATM 2463  O    HOH W  72    10.637  49.177  41.195  1.00  26.01         O
HETATM 2464  O  · HOH W  73     6.040  54.611  40.359  1.00  25.36         O
HETATM 2465  O    HOH W  74    14.418  65.907  30.604  1.00  23.88         O
HETATM 2466  O    HOH W  75    -8.510  49.945  14.056  1.00  24.10         O
HETATM 2467  O    HOH W  76     8.863  56.217   8.553  1.00  27.89         O
HETATM 2468  O    HOH W  77    14.236  68.903   7.657  1.00  18.02         O
HETATM 2469  O    HOH W  78    13.673  73.981  19.313  1.00  23.06         O
HETATM 2470  O    HOH W  79     2.655  61.203  33.265  1.00  24.78         O
HETATM 2471  O    HOH W  80    16.081  49.559  38.301  1.00  22.19         O
HETATM 2472  O    HOH W  81    31.264  56.428  -3.845  1.00  28.22         O
HETATM 2473  O    HOH W  82    15.278  70.852  -9.834  1.00  23.37         O
HETATM 2474  O    HOH W  83    12.293  67.306  31.014  1.00  30.13         O
HETATM 2475  O    HOH W  84     1.153  67.896  23.680  1.00  26.47         O
HETATM 2476  O    HOH W  85     4.177  54.962  -5.513  1.00  26.51         O
HETATM 2477  O    HOH W  86     0.828  56.666  31.132  1.00  26.85         O
HETATM 2478  O    HOH W  87  · 28.043  58.100  16.860  1.00  25.80         O
HETATM 2479  O    HOH W  88     1.418  59.141  31.864  1.00  24.54         O
HETATM 2480  O    HOH W  89     5.171  72.267   6.832  1.00  24.31         O
HETATM 2481  O    HOH W  90    11.102  55.346   6.358  1.00  24.68         O
HETATM 2482  O    HOH W  91    24.301  57.703   7.432  1.00  30.45         O
HETATM 2483  O    HOH W  92  ·  -9.909  65.963  19.571  1.00  23.47         O
HETATM 2484  O    HOH W  93     6.056  67.397   5.777  1.00  31.74         O
HETATM 2485  O    HOH W  94    -2.434  68.992  20.904  0.65  22.09         O
HETATM 2486  O    HOH W  95     8.275  64.974  36.309  1.00  27.28         O
HETATM 2487  O    HOH W  96     1.335  63.466  32.967  1.00  25.70         O
HETATM 2488  O    HOH W  97    -6.025  55.405  29.089  1.00  30.79         O
HETATM 2489  O    HOH W  98    10.185  36.392  30.992  1.00  31.63         O
HETATM 2490  O    HOH W  99    23.569  63.098  31.944  1.00  29.40         O
HETATM 2491  O    HOH W 100    -3.299  51.801  26.540  1.00  34.71         O
HETATM 2492  O    HOH W 101     6.351  62.723  -5.112  1.00  24.63         O
HETATM 2493  O    HOH W 102    14.594  69.684  20.375  1.00  24.27         O
HETATM 2494  O    HOH W 103    18.743  56.475   6.996  1.00  33.37         O
HETATM 2495  O    HOH W 104    12.569  39.880  15.153  1.00  30.55         O
HETATM 2496  O    HOH W 105    27.530  56.419   6.333  1.00  29.29         O
HETATM 2497  O    HOH W 106    26.134  39.160  -1.955  1.00  28.24         O
HETATM 2498  O    HOH W 107     2.711  60.861   7.995  1.00  27.06         O
HETATM 2499  O    HOH W 108     0.449  71.907  21.641  1.00  22.02         O
HETATM 2500  O    HOH W 109    24.328  60.651  -0.284  1.00  26.84         O
HETATM 2501  O    HOH W 110     0.105  36.807  21.145  1.00  35.25         O
HETATM 2502  O    HOH W 111     9.424  67.684   3.202  1.00  25.03         O
HETATM 2503  O    HOH W 112     9.870  65.101 -16.111  1.00  25.20         O
HETATM 2504  O    HOH W 113     0.331  62.672   7.998  1.00  25.35         O
HETATM 2505  O    HOH W 114    30.604  62.219  -3.326  1.00  31.23         O
HETATM 2506  O    HOH W 115    -8.461  62.947  13.452  1.00  31.44         O
HETATM 2507  O    HOH W 116     0.681  36.393  25.982  1.00  28.56         O
HETATM 2508  O    HOH W 117    15.503  50.561  40.707  1.00  28.73         O
HETATM 2509  O    HOH W 118    19.149  69.912  -4.488  1.00  26.57         O
HETATM 2510  O    HOH W 119    16.712  54.018   3.490  1.00  33.99         O
HETATM 2511  O    HOH W 120    14.544  43.323  35.404  1.00  30.45         O
HETATM 2512  O    HOH W 121     0.237  42.592  29.396  1.00  33.25         O
HETATM 2513  O    HOH W 122    22.577  64.264  25.463  1.00  25.91         O
HETATM 2514  O    HOH W 123    18.504  66.572  28.714  1.00  28.19         O
HETATM 2515  O    HOH W 124     6.514  43.992  34.159  1.00  32.12         O
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FIGURE 4PP

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HETATM 2516  O    HOH W 125     21.741  53.968  30.148  1.00 35.71          O
HETATM 2517  O    HOH W 126     20.388  60.636 -14.106  1.00 28.55          O
HETATM 2518  O    HOH W 127      3.717  52.185  -6.457  1.00 32.44          O
HETATM 2519  O    HOH W 128      4.097  75.012  20.095  1.00 26.13          O
HETATM 2520  O    HOH W 129     20.712  67.953   7.909  1.00 30.55          O
HETATM 2521  O    HOH W 130      2.616  71.475   7.389  1.00 32.66          O
HETATM 2522  O    HOH W 131     -3.968  46.144  35.287  1.00 27.82          O
HETATM 2523  O    HOH W 132     -6.231  58.370  29.959  1.00 34.83          O
HETATM 2524  O    HOH W 133     -9.573  70.666  20.525  1.00 35.61          O
HETATM 2525  O    HOH W 134     18.376  48.194 -10.777  1.00 31.13          O
HETATM 2526  O    HOH W 135      7.392  64.158 -14.488  1.00 28.92          O
HETATM 2527  O    HOH W 136     -9.806  64.044  22.839  1.00 30.94          O
HETATM 2528  O    HOH W 137     15.177  36.015  24.066  1.00 35.95          O
HETATM 2529  O    HOH W 138      0.207  36.075  18.248  1.00 30.22          O
HETATM 2530  O    HOH W 139     -5.121  66.714  13.239  1.00 30.64          O
HETATM 2531  O    HOH W 140     14.190  49.167  -9.420  1.00 34.64          O
HETATM 2532  O    HOH W 141      5.829  50.276   8.950  1.00 30.03          O
HETATM 2533  O    HOH W 142     -9.815  56.521   9.803  1.00 35.50          O
HETATM 2534  O    HOH W 143     21.370  40.122  30.064  1.00 39.91          O
HETATM 2535  O    HOH W 144      3.787  42.583  30.403  1.00 28.56          O
HETATM 2536  O    HOH W 145     10.595  57.142   1.988  1.00 27.77          O
HETATM 2537  O    HOH W 146      9.293  72.366  21.198  1.00 32.26          O
HETATM 2538  O    HOH W 147     18.066  45.436   6.890  1.00 38.15          O
HETATM 2539  O    HOH W 148     23.958  58.334  22.474  1.00 29.68          O
HETATM 2540  O    HOH W 149     16.270  43.356  10.738  1.00 33.04          O
HETATM 2541  O    HOH W 150     15.902  68.409   3.393  1.00 34.28          O
HETATM 2542  O    HOH W 151    -11.961  62.595  22.500  1.00 32.46          O
HETATM 2543  O    HOH W 152     -1.772  42.002  27.213  1.00 26.41          O
HETATM 2544  O    HOH W 153      8.485  49.605  -3.375  1.00 33.62          O
HETATM 2545  O    HOH W 154      6.448  64.907   5.091  1.00 35.35          O
HETATM 2546  O    HOH W 155     22.084  47.121  20.652  1.00 40.36          O
HETATM 2547  O    HOH W 156     31.367  37.760  -3.224  1.00 32.70          O
HETATM 2548  O    HOH W 157     23.401  64.152   1.455  1.00 32.23          O
HETATM 2549  O    HOH W 158     21.582  37.129  -8.471  1.00 29.98          O
HETATM 2550  O    HOH W 159     18.428  47.952   5.926  1.00 29.28          O
HETATM 2551  O    HOH W 160     17.740  53.594 -15.170  1.00 29.87          O
HETATM 2552  O    HOH W 161      3.010  72.509  22.439  1.00 32.98          O
HETATM 2553  O    HOH W 162     -2.553  63.775   6.938  1.00 38.56          O
HETATM 2554  O    HOH W 163     25.532  57.079 -11.112  1.00 35.81          O
HETATM 2555  O    HOH W 164     28.315  37.655  -1.292  1.00 32.11          O
HETATM 2556  O    HOH W 165     19.005  69.557   6.373  1.00 34.06          O
HETATM 2557  O    HOH W 166     26.973  52.660  11.997  1.00 40.44          O
HETATM 2558  O    HOH W 167     28.399  59.190   8.790  1.00 36.67          O
HETATM 2559  O    HOH W 168     12.457  68.215   0.508  1.00 32.73          O
HETATM 2560  O    HOH W 169     -6.664  47.822  33.009  1.00 30.45          O
HETATM 2561  O    HOH W 170    -10.120  66.890  17.047  1.00 37.90          O
HETATM 2562  O    HOH W 171     -6.174  74.062  17.486  1.00 37.11          O
HETATM 2563  O    HOH W 172     24.866  61.899  -9.630  1.00 33.35          O
HETATM 2564  O    HOH W 173     15.943  72.397   8.430  1.00 32.03          O
HETATM 2565  O    HOH W 174     13.398  49.109   8.104  1.00 35.44          O
HETATM 2566  O    HOH W 175     29.400  55.940   4.353  1.00 33.32          O
HETATM 2567  O    HOH W 176     30.471  49.195   8.045  1.00 37.82          O
HETATM 2568  O    HOH W 177     37.568  43.862  -4.195  1.00 41.27          O
HETATM 2569  O    HOH W 178      7.449  59.978  36.472  1.00 36.16          O
HETATM 2570  O    HOH W 179     -7.307  64.765  15.029  1.00 35.23          O
HETATM 2571  O    HOH W 180     12.538  46.698  39.295  1.00 36.56          O
HETATM 2572  O    HOH W 181     22.634  65.617  30.960  1.00 34.02          O
HETATM 2573  O    HOH W 182     -0.544  57.001  -5.760  1.00 34.80          O
HETATM 2574  O    HOH W 183     26.267  40.539   0.289  1.00 40.60          O
HETATM 2575  O    HOH W 184      3.841  35.275  15.463  1.00 36.73          O
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FIGURE 4QQ

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HETATM 2576  O    HOH W 185     25.012  64.020  18.977  1.00 34.92           O
HETATM 2577  O    HOH W 186     12.035  58.791 -17.936  1.00 45.62           O
HETATM 2578  O    HOH W 187     17.813  69.407  19.365  1.00 32.09           O
HETATM 2579  O    HOH W 188     21.592  69.401 -10.464  1.00 35.28           O
HETATM 2580  O    HOH W 189      3.273  73.522  24.886  1.00 38.36           O
HETATM 2581  O    HOH W 190      6.976  76.851  10.508  1.00 38.77           O
HETATM 2582  O    HOH W 191      8.681  74.921  10.334  1.00 38.77           O
HETATM 2583  O    HOH W 192     27.748  49.411   9.534  1.00 40.05           O
HETATM 2584  O    HOH W 193     25.094  45.375  11.303  1.00 38.80           O
HETATM 2585  O    HOH W 194     14.543  69.038  24.470  1.00 32.84           O
HETATM 2586  O    HOH W 195     32.510  54.900  -9.840  1.00 45.77           O
HETATM 2587  O    HOH W 196      8.698  67.456  -5.183  1.00 35.92           O
HETATM 2588  O    HOH W 197     16.502  69.545   5.737  1.00 38.64           O
HETATM 2589  O    HOH W 198     -7.354  63.246  11.247  1.00 39.32           O
HETATM 2590  O    HOH W 199    -12.028  68.718  21.648  1.00 33.50           O
HETATM 2591  O    HOH W 200     -6.896  67.904  14.804  1.00 39.42           O
HETATM 2592  O    HOH W 201     24.429  58.682  28.796  1.00 32.80           O
HETATM 2593  O    HOH W 202     20.994  45.374  22.270  1.00 43.18           O
HETATM 2594  O    HOH W 203     27.768  36.163   0.789  1.00 37.93           O
HETATM 2595  O    HOH W 204     12.107  70.493   5.353  1.00 31.16           O
HETATM 2596  O    HOH W 205      8.004  80.542  17.728  1.00 38.22           O
HETATM 2597  O    HOH W 206      7.479  80.021  13.490  1.00 34.21           O
HETATM 2598  O    HOH W 207     11.897  75.857  22.951  1.00 41.33           O
HETATM 2599  O    HOH W 208     19.816  71.916  17.196  1.00 44.96           O
HETATM 2600  O    HOH W 209     25.642  64.112  -8.802  1.00 44.32           O
HETATM 2601  O    HOH W 210     18.952  66.778  25.999  1.00 37.54           O
HETATM 2602  O    HOH W 211     -0.655  38.452  17.557  1.00 38.45           O
HETATM 2603  O    HOH W 212    -12.764  62.388   9.560  1.00 36.35           O
HETATM 2604  O    HOH W 213     21.845  74.994  14.861  1.00 41.32           O
HETATM 2605  O    HOH W 214     30.786  53.281   7.250  1.00 44.09           O
HETATM 2606  O    HOH W 215      7.793  52.413   8.548  1.00 41.95           O
HETATM 2607  O    HOH W 216     30.863  53.890   4.624  1.00 38.22           O
HETATM 2608  O    HOH W 217     -4.781  72.462  14.360  1.00 41.00           O
HETATM 2609  O    HOH W 218     -0.870  68.104   6.236  1.00 39.73           O
HETATM 2610  O    HOH W 219     13.650  58.218  39.241  1.00 40.58           O
HETATM 2611  O    HOH W 220      1.493  66.322   6.500  1.00 45.88           O
HETATM 2612  O    HOH W 221     23.567  56.278 -16.417  1.00 34.33           O
HETATM 2613  O    HOH W 222     23.046  34.837  17.272  1.00 39.62           O
HETATM 2614  O    HOH W 223     -8.109  59.892  28.916  1.00 37.82           O
HETATM 2615  O    HOH W 224     10.352  42.254   9.975  1.00 39.29           O
HETATM 2616  O    HOH W 225     18.885  35.203  16.703  1.00 44.51           O
HETATM 2617  O    HOH W 226     12.946  69.611  26.650  1.00 34.69           O
HETATM 2618  O    HOH W 227      7.058  35.692  13.366  1.00 37.88           O
HETATM 2619  O    HOH W 228    -13.267  54.430  15.645  1.00 23.80           O
HETATM 2620  O    HOH W 229     12.963  69.458  -3.453  1.00 35.08           O
HETATM 2621  O    HOH W 230     33.510  49.606  -4.025  1.00 30.23           O
HETATM 2622  O    HOH W 231     16.160  59.023  39.473  1.00 35.64           O
HETATM 2623  O    HOH W 232     12.557  56.102  40.090  1.00 43.14           O
HETATM 2624  O    HOH W 233     13.800  72.882  10.589  1.00 34.37           O
HETATM 2625  O    HOH W 234     20.533  67.069  23.261  1.00 37.64           O
HETATM 2626  O    HOH W 235     17.817  67.874  23.169  1.00 43.45           O
HETATM 2627  O    HOH W 236     10.472  63.084 -17.699  1.00 44.86           O
HETATM 2628  O    HOH W 237     24.573  38.270  21.430  1.00 35.75           O
HETATM 2629  O    HOH W 238     12.284  67.555  -2.962  1.00 38.23           O
HETATM 2630  O    HOH W 239     14.642  70.486  -3.593  1.00 41.27           O
HETATM 2631  O    HOH W 240     12.690  72.444  -4.729  1.00 38.59           O
HETATM 2632  O    HOH W 241     10.269  78.965  17.530  1.00 34.88           O
END
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FIGURE 4RR

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